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STUDIES ON THE METABOLISM OF OBESITY

I. THE RELATION BETWEEN FOOD INTAKE AND BODY WEIGHT IN SOME OBESE PERSONS *

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INTRODUCTION

There is a difference, at least in degree, between obesity and overweight. Overweight usually results from overfeeding, sedentary habits or a combination of both. Certain cases of obesity unquestionably follow the same causes, but just as unquestionably other cases of obesity are seen which show neither excessive food intake nor lessened energy expense. In such persons the tendency to accumulate and deposit fat seems to be entirely independent of any of the usual causes of increased weight. Both overeating and underexercise are common faults of mankind, yet excessive obesity is comparatively rare. On the other hand, one sees a fairly large number of healthy but thin persons whose food intake is in excess of their calculated caloric requirements, yet who cannot gain weight under any circumstances. The conclusion seems almost inevitable that the maintenance of body weight may be practically independent of the caloric balance, and that obesity may result from causes other than excessive food intake or diminished energy expense.

To ascertain if possible the cause or causes of "unexplained" obesity prompted us, in 1920, to begin a series of planned metabolic experiments along definite lines. Up to the present time we have studied: 1. The food intake of cases of obesity under dietary control. 2. The basal metabolism in obesity. 3. The specific dynamic effect of various foods.[1]

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* From the Medical Clinic, the Otto Baer Fund for Clinical Research, and the Nelson Morris Memorial Institute for Medical Research of the Michael Reese Hospital.

1. Strouse, Solomon: Carbohydrate Oxidation in Relation to Body Weight, Proc. Am. Soc. for Clinic Investigation, 1921, p. 35; Strouse, Solomon; Wang, C. C., and Dye, M.: The Food Metabolism of Obesity, Proc. Inst. Med., Chicago **4**:169, 1923; Studies on the Metabolism of Obesity. Preliminary Report, J. A. M. A. **82**:2111 (June 28) 1924.

The present report deals with the question of food intake in obesity.

Von Noorden [2] divided obesity cases as follows:

1. "Mast-fettsucht" due to *a*, overfeeding; *b*, underwork ("Faulheitsfettsucht"); *c*, a combination of overfeeding and underwork.

2. Thyrogenous obesity due to lowered energy exchange: *a*, Primary; *b*, secondary, complicated by involvement of other organs like the pancreas, genitalia, hypophysis, etc. Later study of the basal metabolism in obesity cast doubt on the thyrogenous origin of von Noorden's Group 2 *b*, or secondary thyrogenous obesity, and most students classify this group as:

3. Constitutional obesity. This simply means that the person becomes obese not from overeating, underexercise, or hypothyroid disease, but because of a "constitutional" tendency to obesity. This, of course, is merely giving a name to an unexplained phenomenon.

REVIEW OF THE LITERATURE

Recently considerable literature has accumulated on the relation of obesity to diseases of various ductless glands, and in this connection we wish to state that in not a single instance during the four years of this work have we used endocrine terminology in defining obesity. Since our work was directed entirely toward a metabolic explanation of obesity, descriptive terms binding the individual case to one or more ductless glands seemed foreign to our purpose. In order to obtain objective readings, no clinical interpretation was made on persons sent to the laboratory for study, beyond noting the extent of overweight; and it was not until the laboratory workers had completed and tabulated their results that the clinical notes were consulted and an effort made to correlate the findings. The results of this comparative study will be found in a later paper of this series (to be published).

Many cases of so-called constitutional obesity are reported in the literature. Von Noorden [3] reports the case of a man aged 39, who weighed 102 kg., and who, exercising freely in the open air, was kept for three months on a diet of 1,720 calories or less and who lost only 1 kg. His actual caloric requirements should have been near 2,700 calories. A control case weighing 98 kg., exercising less actively, lost 4.8 kg. in four weeks on the same diet. Von Noorden also reports the case of a woman aged 65, weighing 86 kg., who gained 0.5 kg. in six weeks on a diet equivalent to from 900 to 1,000 calories. Schwenkenbecher [4]

2. Von Noorden, C.: Ueber die vershiedenen Formen der Fettsucht, Med. Klin. **5**:1, 1909.

3. Von Noorden, C.: Die Fettsucht, Nothnagel's Spezielle Pathologie und Therapie, Vienna, A. Hölder, 1900.

4. Schwenkenbecher: Ueber die Ausscheidung des Wassers durch die Haut, Deutsch. Arch. f. klin. Med. **79**:29, 1904.

studied two obese girls, one of whom began to lose weight only when the food was reduced to 17 calories per kilogram of body weight (total caloric intake, 1,020).

Saloman,[5] in von Noorden's clinic, carefully studied an obese girl, aged 16, who weighed 71.4 kg. and who gained 0.5 kg. in eight days on a controlled diet of 1,300 calories. During this period she had plenty of open-air exercise. By maintaining the diet at 1,900 calories for some months her weight remained constant.

The more recent and extensive metabolic studies make possible recalculation of figures of earlier work and give a better basis for comparison with normal persons. Du Bois'[6] method of calculating body surface, and the prediction tables of Harris and Benedict,[7] give a standard of comparison now generally accepted as more accurate than any previous standards. In some of the cases quoted here we have recalculated the data to conform to the normal standards of Du Bois or of Harris and Benedict.

Loewy and Hirschfeld,[8] studying the so-called constitutional obesity, report the case of a man, aged 43, weighing 64 kg., height 165 cm., who did "heavy work" for two periods of nine and six days each on diets equivalent to from 2,210 to 2,320 calories containing from 70 to 74 gm. of protein. According to the Du Bois standard his basal requirements were 1,620 calories, and his working requirements then should have been a minimum of 2,500 calories. They report a second case of an obese woman, aged 45, who weighed 55 kg. and whose height was 149 cm., who kept at work without losing weight for five days on a diet of 1,380 to 1,570 calories. Her basal requirements on the Du Bois scale were 1,328 calories.

Grafe and Graham[9] made a metabolic study lasting 107 days on a young dog, varying the food intake from a hunger period to a long period, during which time the average daily food intake was 210 per cent., the minimum basal metabolism. They found the weight constant "with very slight variations." They quote the old experiment

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5. Salomon: Ueber Durstkuren, Von Noorden's Klinische Abhanddlungen **6**. 1905.

6. Du Bois, D., and Du Bois, E. F.: A Formula to Estimate the Approximate Surface Area If Height and Weight Be Known, Arch. Int. Med. **17**:863 (June) 1916.

7. Harris, J. A., and Benedict, F. G.: A Biometric Study of Basal Metabolism in Man, Carnegie Inst. Wash., No. 279, 1919.

8. Loewy, A., and Hirschfeld, F.: Beobachtungen ueber das Minimum des Erhaltungsumsatzes. Ein Beitrag zur Frage der sogenannten konstitutionellen Fettsucht, Deutsch. med. Wchnschr. **36**:1794, 1910.

9. Grafe, E., and Graham, D.: Ueber die Anpassungsfähigkeit des tierischen Organismus an überreichliche Nahrungszufuhr, Ztschr. f. Physiol. Chem. **73**:1, 1911.

of Neuman [10] on himself, who, for an almost steady period of two years maintained weight and well-being on diets equivalent to 1,766, 2,199 and 2,403 calories. From their studies Grafe and Graham concluded that caloric intake and energy expense do not always account for the weight curve of human beings.

Grafe and Koch,[11] studying the effect of prolonged overfeeding on metabolism, cited one remarkable instance of weight maintenance despite large variations in caloric intake. A boy, aged 14 years, weighing 26.5 kg., whose height was 140 cm., was kept for ten days on a diet of 88 calories per kilogram of body weight, then fourteen days on 51 calories per kilogram of body weight without any change in the weight curve. This was followed by another ten day period of 40 calories per kilogram of body weight, during which period he lost only 0.5 kg.

Umber [12] claimed to have studied some obese persons for long periods, paying attention to caloric intake, fluid balance and weight, and to have found many such with lowered "energy exchange." He cites the case of an obese woman, aged 61, who weighed 96 kg. and whose height was 150 cm. (basal metabolism, Du Bois, 1,491 calories daily), who lived on 1,200 gm. of milk daily (equal to about 800 calories) for thirty-nine days and who lost only 0.5 kg. Later, for seven days she received 919 calories daily containing 10.3 gm. nitrogen. She gained 7.2 gm. nitrogen, but her weight remained at 96 kg., which means that she maintained body weight on 9.6 calories per kilogram of body weight. Umber also reports a case which, from the clinical description (no basal metabolism study) belonged to the group of hypothyroids. A woman, aged 45, weight 97.7 kg., height 163 cm. (basal metabolism, Du Bois, 1,815 calories), who for twelve days had the equivalent of 1,000 calories, for six days 800 calories and who remained in nitrogen balance and maintained weight. He reports a third case of apparently hypophyseal obesity in a boy, aged 12, weight 96 kg., height 156 cm. (basal metabolism, Benedict and Talbot,[13] 1,850 calories), who kept his weight on 1,600 calories.

Düring's [14] studies led him to believe that, in constitutional obesity, loss of weight paralleled water and salt excretion, an opinion shared

10. Neuman, R. O.: Arch. f. Hyg. **45**:1, 1902, quoted by Grafe and Graham.

11. Grafe, E., and Koch, R.: Ueber den Einflusz langdauernder starker Uebernährung auf die Intensität der Verbrennungen im menschichen Organismus (Untersuchungen bei Mastkuren), Deutsch. Arch. f. klin. Med. **106**:564, 1912.

12. Umber: Konstitutionelle Fettsucht und innere Sekretion, Med. Klin. **9**: 2014, 1913.

13. Benedict, F. G., and Talbot, F. B.: Metabolism and Growth from Birth to Puberty, Carnegie Inst. Wash. No. 320, 1921.

14. Düring, M.: Ueber Störungen des Flüssigskeits und Salzgleichgeweichts bei gewissen Fällen der sogenannter "konstitutionellen Fettsucht," Cor.-Bl. f. schweiz. Aerzte **44**:1425, 1914.

by Grafe.[15] Grafe studied several cases in which no loss of weight occurred, even following the intake of food of very low caloric value.

Talbot [16] studied the metabolism of a very obese child with a small sella turcica and gives the following figures: A boy, aged 2 years and 9 months, weighed 24.8 kg., whose height was 94 cm., body surface was 0.879 sq. cm. The average daily caloric intake for three weeks was 895 and the child gained weight. The normal requirement, as figured by Talbot, was 1,200 calories. On from 700 to 800 calories the child lost weight. His basal metabolism varied from 1,046 calories when awake to 677 when asleep. It was minus 41 per cent. compared to age, and minus 32 per cent. compared to weight.

Rahe and Plaut,[17] studying the effect of food poor in protein, report the case of a man aged 40, of normal build, who weighed 67 kg. and whose height was 168 cm., who on a diet of between 1,000 and 1,300 calories, gained 5 kg. in nineteen days (basal metabolism on the Harris and Benedict tables is 1,558 calories). This followed a period of undernutrition, and may be explained on the basis of the lowered metabolism which has been found to follow such periods.

EXPERIMENTAL DATA

From this review of the available literature it is apparent that obesity can and does occur in persons without showing any direct relation to food intake. Our own experience had led us to believe that underweight in otherwise healthy persons also occurs even when the caloric intake is more than sufficient to supply energy demands. Speaking metabolically, the "constitutional" obese and the healthy underweight may represent extremes of the same problem.

REPORT OF CASES

CASE 1.—Our first experiment was a clinical test on a very thin, healthy man, aged 39, weighting 52 kg., and whose height was 175 cm. He was a very active worker, a physician, who ate normal food and slept from six to seven hours out of the twenty-four. On a four weeks' vacation he increased his food intake approximately 50 per cent., mainly in carbohydrates, he slept from ten to fourteen hours a day, took no violent exercise, and spent most of the time lying on a hammock on the porch engaged in reading current nonmedical magazines and novels. Although excessively fatigued at the beginning of the vacation and decidedly refreshed at the end of the four weeks, his weight

15. Grafe, E.: Zur Pathologie und Therapie der sogenant. "konstitutionellen Fettsucht," Deutsch. Arch. f. klin. Med. **133**:41, 1920.

16. Talbot, F. B.: The Metabolism of a Very Obese Child with a Small Sella Turcica (Typus Frölich?), Am. J. Dis. Child. **20**:331 (Oct.) 1920.

17. Rahe, F., and Plaut, R.: Zur Frage Eiweiss-armer Ernährung. Deutsch. Arch. f. klin. Med. **137**:187, 1921.

remained constant. Surely if his weight were dependent on the caloric equation, the four weeks of overfeeding and underexercise, coupled with the removal of the nervous activity of his vocation, should have resulted in a gain of weight.

Case 2.—A young woman, aged 30, whose height was 165 cm., and whose weight was 86.8 kg., the subject of much of our first two years' work was very eager to cooperate and very reliable. She had a scale at home, to the use of which she was accustomed through feeding her diabetic mother. All articles of food were weighed and noted in a book from which the food values were subsequently calculated by us. She had been obese for years and showed other signs of supposed endocrine disturbance (amenorrhea, hair on face). She said that she was a very light eater, and all her life she had been a hard worker. At the time of the experiment she "kept house" for the family, doing all the cooking, cleaning, and general housework including floor scrubbing, in addition

Table 1.—*The Weight and Calories of Case 2*

Date	Calories	Weight, Kg.	Date	Calories	Weight, Kg.
9/ 2/21	849	86.8	12/21/21	593	....
9/ 3/21	1,131	....	12/22/21	565	....
9/ 4/21	1,116	....	12/23/21	888	....
9/ 5/21	1,658	....	12/24/21	837	....
9/ 6/21	630	....	12/25/21	974	....
9/ 7/21	669	....	12/26/21	696	....
10/24/21	803	83.7	12/27/21	489	....
11/27/21	1,672	84.1	1/10/22	2,143*	....
12/19/21	1,007	....	1/11/22	1,742	....
12/20/21	1,088	....	1/12/22	.....	85.6

* Candy spree.

Table 2.—*Case of Girl With Appearance of Gigantism*

Date, 1923	Diet				Urine Nitrogen	Weight, Kg.
	Protein	Fat	Carbohydrate	Calories		
September 20	98	98	150	1,874	....	104.5
September 21	84	94	150	1,782	....	.....
September 22	85	107	98	1,695	....	105
September 23	84	91	134	1,691	....	.....
September 24	82	90	110	1,578	13.6	104.5
September 25	81	101	111	1,687	13.6	.....
September 26	84	108	124	1,804	12.3	105
September 27	89	127	128	2,011	13.1	....
September 28	86	91	129	1,687	8.4	104.5
September 29	82	108	125	1,606	14.3	.....
September 30	90	75	90	1,395	12.6	103.1
October 1	89	71	88	1,347	15.8	.....
October 2	89	76	90	1,395	16.9	104
October 3	88	74	79	1,334	16.5	.....
October 4	89	76	90	1,395	17.6	.....
October 5	90	75	90	1,395	12.8	106

to acting as nurse and dietician for her diabetic mother. Previous notes on her food intake seemed to indicate such a low caloric value as to make a weighed dietary study of particular interest. Basal metabolism 1,526 calories.

It will be noted that, except for the two days of her candy spree, the calculated dietary periods were considerably under her basal metabolic requirements. These periods represent no special time, but are typical of the food she took as an average diet while at hard labor. It should be recalled here that statistics on heart disease show that from the standpoint of incidence of heart disease, the "housework" of the woman without domestic help places her in the same class as the laborer. The very slight changes in the weight curve are also typical of what the patient had found out for herself, that her weight did not depend on the amount of food she ate.

Case 3.—A girl, aged 15, who weighed 105 kg., with the appearance of gigantism, whose height was 177 cm.; had basal metabolism of 1,844, 4.6 per cent.

below normal of 1,933, was under hospital observation for a period of sixteen days on a weighed diet. At no time during the study was the patient confined to her bed, but she was allowed the freedom of the floor. Careful observation convinces us that she ate no more than was indicated by the figures. Almost every day food was returned, and the chart indicated the only food eaten. It will be seen that she maintained her weight for sixteen days on a diet considerably below her basal requirements, and at the end of the experiment weighed 1.5 kg. more than at the beginning.

Case 4.—R. K., a woman, aged 26, whose weight was 78.3 kg., and whose height was 148.5 cm., had been under our observation for several years and

Table 3.—*Obese Woman With Vaginal Bleeding*

Date, 1923	Protein	Fat	Carbohydrate	Calories	Urinary Nitrogen	Weight Lb.	Weight Kg.	Vaginal Bleeding	Medication
11/19	50	51	101	1,063	18.03	167	76	++	Desiccated thyroid, ½ grain; desiccated whole pituitary, 1 grain; corpus luteum, 5 grains; three times daily by mouth
11/20	50	50	100	1,050	7.45	....	..	++	
11/21	50	49	99	1,037	7.64	....	..	0	
11/22	51	49	100	1,055	10.56	165	75	0	
11/23	50	50	101	1,054	8.91	....	..	0	
11/24	50	50	101	1,054	8.5	....	..	+	
11/25	50	50	100	1,056	6.9	....	..	+	
11/26	50	50	100	1,050	4.65	162	73.7	+	Desiccated whole pituitary, 1 grain; corpus luteum, 5 grains; three times daily by mouth
11/27	51	50	101	1,058	2.68	....	..	+	
11/28	50	50	101	1,054	8.81	....	..	0	
11/29	50	50	99	1,046	8.85	161.5	73.5	+	
11/30	51	51	100	1,063	6.60	....	..	+	
12/ 1	51	51	100	1,063	6.13	....	..	+	
12/ 2	51	50	101	1,058	5.88	....	..	+	Obstetric pituitary extract hypodermically daily *
12/ 3	50	51	100	1,059	7.97	160	72.8	+	
12/ 4	49	50	100	1,046	10.45	....	..	+	
12/ 5	50	50	100	1,050	11.53	....	..	0	Obstetric pituitary extract, corpus luteum, hypodermically daily *
12/ 6	47	29	86	798	.....	161	73.4	+	
12/ 7	49	33	95	873	.....	....	..	+	
12/ 8	50	50	100	1,050	8.29	....	..	+	
12/ 9	50	51	100	1,059	9.51	....	..	+	
12/10	50	51	100	1,059	7.15	157.5	71.6	0	
12/11	50	50	100	1,050	11.33	....	..	0	Desiccated thyroid; 1 grain three times daily by mouth
12/12	50	50	100	1,050	8.37	....	..	0	
12/13	50	50	100	1,050	7.87	156	71	0	
12/14	50	50	100	1,050	.....	155.5	70.7	0	
12/15	52	50	100	1,058	.....	....	..	0	

* Size of ampule used, 1 cubic centimeter.

Table 4.—*Case of Woman Given to Overeating*

	Calories	Weight Lb.	Weight Kg.
11/2/21	564	151.5	68.8
11/3/21	427	.....	....
11/4/21	750	.....	....
11/5/21	720	.....	....
11/6/21	885	.....	....
11/7/21	477	.. ..	....
11/8/21	523	148.5	67.5

always maintained a steady weight on a low caloric diet. She was admitted to the hospital in November, 1923, because of excessive vaginal bleeding for which no local cause could be found. Because of difficulty in keeping her in the hospital without treatment, the dietary study is complicated by the administration of various glandular extracts. Her basal metabolism was 1,934; her activities in the ward should have raised her energy requirements approximately 30 per cent. For a period of one month her diet was approximately 1,050 calories, 84 per cent. less than her basal requirements, more than 100 per cent. less than her calculated needs. The weight curve (Table 3) shows a loss of 1 kg. during

the first four days, then a practically steady curve for fifteen days, followed by a more definite loss during an eight day period of thyroid feeding (desiccated thyroid, 3 grains daily).

CASE 5.—A perfectly healthy "stout" woman, frankly given to overeating and underexercising, with a normal basal metabolism, wished to be reduced.

The interesting feature in this patient lies in the very low caloric intake necessary to reduce her weight 1.3 kg. in eight days. Metabolism studies showed perfectly normal metabolism at the beginning and end of the experiment, except that the respiratory quotient, after the eight days of subcaloric diet, indicated oxidation of body fat. This of course was to be expected under the conditions of the experiment.

SUMMARY

1. The literature on obesity is reviewed to prove the existence of an entity, which for want of a better name is called constitutional obesity.

2. Persons showing this predisposition show no interdependence between food intake, energy expense and weight.

3. Dietary studies of some new cases are given; also a clinical study of a healthy, very thin man is given.

4. The data thus accumulated definitely prove that certain types of obese persons maintain their weight without regard to the usually accepted caloric balance.

STUDIES ON THE METABOLISM OF OBESITY

II. BASAL METABOLISM *

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In the first communication we showed both by quotations from the literature and by our experiments that certain obese persons maintained body weight on diets below their calculated caloric requirements.[1] To explain this apparent anomalous balance between caloric intake and energy expense, we made an intensive study of the specific dynamic action of foods in persons of widely varying body build. The results of this study will be published shortly. A rather large and interesting series of basal metabolism readings were accumulated during this research, and since the subject of the basal metabolism in obesity cannot be considered closed we present in this paper our data on the basal metabolism in obesity.

REVIEW OF THE LITERATURE

Before the development of modern methods of studying gaseous exchange and the accumulation of more accurate standards of comparison, the literature on the metabolism of obesity contains much conjecture and a few isolated studies. In 1897 Magnus-Levy [2] studied the basal metabolism of fourteen cases of obesity, and found no change except in myxedema, in which condition he found lowered basal metabolism. Jaquet and Svenson,[3] in 1900, suggested that variations in basal metabolism could not explain the metabolic anomaly in obesity, and predicted that study of the twenty-four hour metabolism, including the effect of muscular work, would be necessary. They studied the basal metabolism of three cases in which a normal rate was found.

In 1907 von Noorden [4] speaks of "corpulency due to a slowing in the processes of metabolism" but was able to report only twenty-four

* From the Otto Baer Fund for Clinical Research, and the Gusta Morris Rothschild Fund of the Michael Reese Hospital and the Nelson Morris Institute for Medical Research.

1. Strouse, Solomon, and Dye, M.: Studies on the Metabolism of Obesity. I. The Relation Between Blood Intake and Body Weight on Some Obese Persons, Arch. Int. Med. **34**:267 (Sept.) 1924.

2. Magnus-Levy, A.: Untersuchungen zur Schilddrüsenfrage, Ztschr. f. klin. Med. **3**:269-1897; Der Einfluss von Krankheiten auf den Energiehaushalt im Ruhezustand, Ztschr. f. klin. Med. **60**:177, 1906.

3. Jaquet, A., and Svenson, N.: Zur Kenntnis des Stoffwechsels fettsuchtiger Individuen, Ztschr. f. klin. Med. **41**:375, 1900.

4. Von Noorden, C.: Obesity. Metabolism and Practical Medicine, Anglo-American Edition, Chicago., W. T. Keener & Co., 1907, Vol. 3.

studies of the respiratory exchange, "the whole of the existing records." Von Noorden criticized the correctness of these readings on various technical grounds. Studies of Loewy and Hirschfeld [5] on three obese persons forced them to conclude that, up to their time, no one had proved "lowered energy exchange" in obesity. In 1915 Means [6] again studied the question. He showed that the basal metabolism in two cases of "simple obesity," figured per square meter and by the hour, using the Du Bois formula, was normal; in one case of "hypopituitarism" it was increased, in two other cases (hypopituitary?) it was low. One year later Means [7] says "there is no characteristic change whatsoever in the basal metabolism even in very extreme cases of obesity." Occasionally he noted a slight reduction when clinical evidence of disturbed internal secretion was present. His study embraced twelve cases.

Haussleiter [8] also studied twelve cases and concludes that there are three types of obesity:

TABLE 1.—*Findings in Haussleiter's Case*

Case	Age	Sex*	Weight, Kg.	Height, Cm.	Haussleiter Basal Metabolism	Du Bois Predicted Basal Metabolism
1†	13	..	....	...	.....	.....
2	13	..	67.4	156	2,237	1,992
3	13	♀	69.0	151	1,240	1,879
4	32	♂	79.65	167	2,082	1,810
5	36	♂	88.5	168	2,830	1,906
6‡	..	..	....	...	.....	.....
7	16	♀	38.0	141	1,465	1,198
8	18	♂	64.0	144	1,630	1,272
9	34	♀	83.5	154	1,910	1,594

* In this column, ♀ indicates female, ♂ male.
† Cardiorenal disease with edema.
‡ Oxygen consumption so high that it must be abnormal.

1. Endogenous obesity, with increased basal metabolism.

2. Endogenous obesity with periodic variations of basal metabolism on the lower border of the normal.

3. Endogenous obesity (thyrogenous form), with basal metabolism absolutely lower than the lowest normal.

A careful review of the work of Haussleiter, on the basis of our large experience with metabolic studies on obese persons, forces us to suspect that his experimental conditions could not have been perfect.

5. Loewy, A., and Hirschfeld, F.: Beobachtungen über das minimum des Eraltungsumsatzes. Ein Beitrag zur Frage der sogenannten konstitutionellen Fettsucht, Deutsch. med. Wchnschr. **36**:1794, 1910.

6. Means, J. H.: Studies of the Basal Metabolism in Obesity and Pituitary Disease, J. M. Res. **32**:121, 1915.

7. Means, J. H.: The Basal Metabolism in Obesity, Arch. Int. Med. **17**:704 (May) 1916.

8. Haussleiter, H.: Ueber den Gaswechsel verschiedener Formen von Fettsucht und seine Beeinflussung durch Nahrungsaufnahme, Arbeit und Arzneimittel, Ztschr. f. exper. Path. u. Therap. **17**:413, 1915.

Some of his basal readings recalculated on either DuBois' scale, or according to the Benedict-Harris prediction tables, and compared to the large recent accumulations of normal belong to the group now associated almost entirely with hyperactivity of the thyroid gland.

Because of the difference in the results of Haussleiter's studies and those reported by most other workers, it seems wise to report his cases in more detail.

Talbot [9] reported one very obese child, aged 2 years and 9 months, with Frölich's syndrome, who showed a basal metabolism 41 per cent. below normal compared to age and 32 per cent. compared to weight.

In the large series of normal cases that Benedict and Carpenter [10] studied, are found some with height and weight relationship varying more or less from normal, but the variations in basal metabolism found in their series bear no direct relationship to the body build. For instance, their tallest and thinnest man showed a basal metabolism of 34.9 calories per square meter per hour; their shortest and stoutest subject showed 35.2 calories per square meter per hour; and the variations in apparently normal human beings were from 33.9 to 44.2 calories per square meter and hour.

Grafe,[11] in 1920, expressed the belief that most cases of obesity are not pure expressions of either exogenous or endogenous causes, although one or the other is predominant in each case. His studies on basal metabolism showed great variations.

Plaut [12] studied a large series of normal, obese, and constitutionally thin persons, and found a normal basal metabolism in all cases of obesity except in myxedema and thyrogenous obesity, in which the basal metabolism was lowered. In 1923 [12] she added twenty-six more cases, and arrived at the same conclusion.

EXPERIMENTAL DATA

Our own studies on basal metabolism were incidental to more extensive investigations of the specific dynamic action of foods in cases of obesity. During the season from 1920 to 1921 all the work was done with a Benedict portable respiration apparatus.[13] During this year

9. Talbot, F. B.: The Metabolism of a Very Obese Child with a Small Sella Turcica (Typus Frölich), Am. J. Dis. Child. **20**:331 (Oct.) 1920.

10. Benedict, F. G., and Carpenter, T. M.: Food Ingestion and Energy Transformations, Carnegie Inst. Wash., No. 261, 1918.

11. Grafe, E.: Zur Pathologie und Therapie der sogenannten konstitutionellen Fettsucht, Deutsch. Arch. f. klin. Med. **133**:41, 1920.

12. Plaut, R.: Gaswechseluntersuchungen bei Fettsucht und Hypophysiserkrankungen, Deutsch. Arch. f. klin. Med. **139**:285, 1922; ibid. **142**:266, 1923.

13. Some of this year's work was performed in the laboratory of Home Economics of the University of Chicago, with the active guidance of Prof. Katherine Blunt.

repeated readings were made on a somewhat small group of persons, including both sexes, and of body build varying from extreme thinness in healthy persons to cases of marked obesity. The usually accepted technic was adopted. The subject not having eaten for from twelve to fifteen hours previously, rode to the laboratory, and was given a rest period of at least thirty minutes before the test was started. Basal metabolism was figured entirely on oxygen consumption. Since the fall of 1921, all work has been done with the Tissot gasometer, the gas analyses being made with the Haldane apparatus. The cases are grouped in tables of normal, underweight and overweight subjects, as

TABLE 2.—*Results with the Benedict Apparatus*

							Heat Production					
							Calories per 24 Hours			Calories per Sq. M. per Hour		
Subject	Date	Sex*	Age	Height, Cm.	Weight, Kg.	Deviation from Normal, per Cent.	Observed	Harris-Benedict Prediction	Difference, per Cent.	Observed	Du Bois Formula	Difference, per Cent.
Normal Subjects												
1. P.	2/25/21	♀	27	150.5	51	+ 6	1,190	1,296	−8.9	37.2	37.0	+0.54
2. M.	2/ 1/21	♂	38	176	79.5	+ 8	1,850	1,784	+3.7	38.9	39.5	−1.52
3. L.	3/ 1/21	♀	25	165	61	0	1,600	1,426	+12.1	40.5	37.0	+9.5
Underweights												
4. S.	1/17/21	♂	38	174	51	−28	1,510	1,382	+9.2	39.3	39.5	−0.52
4. S.	1/27/21	♂	38	174	51	−28	1,510	1,382	+9.2			
5. P.	3/18/21	♀	23	170	52	−17	1,352	1,359	0	35.3	37.0	−4.6
6. D.	3/16/21	♂	25	170	59	−11	1,671	1,560	+7.1	41.2	39.5	+4.3
7. K.	3/15/21	♂	25	182	61.4	−19	1,450	1,653	−12.3	33.7	39.5	−14.7
8. Ka.	3/23/21	♀	30	157	50	−12	1,245	1,283	−2.9	35.1	36.5	−3.8
7. K.	1/26/22	♂	26	182	61.4	−20	1,540	1,653	−6.8	35.2	39.5	−10.9
7. K.	2/ 9/22	♂	26	182	61.4	−20	1,510	1,653	−8.7	35.0	39.5	−14.0
4. S.	2/ 7/22	♂	39	174	51	−28	1,425	1,382	+2.9	37.1	39.5	−6.1
Overweights												
9. E. S.	1/28/21	♀	27	165	85	+43	1,810	1,647	+9.9	39.5	37.0	+6.3
10. G.	2/ 7/21	♀	32	153.5	71.5	+29	1,395	1,472	−5.5	34.2	36.5	−6.3
9. E. S.	10/25/21	♀	28	165	83.6	+40.5	1,525	1,628	−6.3	33.4	37.0	−9.7
9. E. S.	11/28/21	..	..	.....	84.1	+41.5	1,685	1,633	+3.2	36.8	37.0	−0.5
9. E. S.	1/12/22	..	..	.....	85.5	+43.7	1,815	1,647	+10.2	39.2	37.0	+5.9
9. E. S.	3/ 8/22	..	..	.....	86.3	+45.0	1,713	1,654	+3.6	36.8	37.0	−0.5
9. E. S.	6/ 1/22	..	..	.....	85.5	+43.7	1,634	1,647	−0.79	35.3	37.0	−4.6
11. Kau.	3/17/21	♀	35	157	79	+35	1,280	1,598	−18.2	29.7	36.5	−18.6
12. Kar.	3/23/21	♂	35	163	70.5	+13.5	1,475	1,612	−8.5	34.9	39.5	−11.6
13. S.	3/27/21	♀	39	177	127	+78	1,860	2,014	−7.7	33.0	36.5	−9.6

* In this column, ♀ indicates female, ♂ male.

determined by comparison with the standards accepted by life insurance companies.[14]

Our results are given in Tables 2 and 3 and are graphically arranged in Chart 1. Table 2 contains the work done with the Benedict portable apparatus, Table 3 that done with the Tissot gasometer. It will be noted that body weight is the only "standard" we use and that our subjects varied from 30 per cent. underweight to 140 per cent. overweight. No attempt is made at this time to make clinical groupings; our sole object was to obtain objective metabolic data on overweight regardless of the cause.

14. Association of Life Insurance Medical Directors and Actuarial Society of America, Medico Actuarial Mortality Investigation, 1912.

All mathematical calculations of heat production are made on the basis of the Harris-Benedict prediction tables, and from the height-weight formula for body surface of Du Bois [15] excepting in the case of a child, aged 12 years (Subject 30, Table 3), whose metabolism

TABLE 3.—*Results with the Tissot Gasometer*

Subject	Date	Sex*	Age	Height, Cm.	Weight, Kg.	Heat Production: Deviation from Normal, per Cent.	Calories per 24 Hours: Observed	Calories per 24 Hours: Harris-Benedict Prediction	Calories per 24 Hours: Difference, per Cent.	Calories per Sq. M. per Hour: Observed	Calories per Sq. M. per Hour: Du Bois Formula	Calories per Sq. M. per Hour: Difference, per Cent.
Normal Subjects												
14. M. S.	4/12/23	♀	21	167.5	62.3	+3.0	1,403	1,463	—4.1	34.4	37.0	— 7.0
14. M. S.	5/16/23	..	..	167.5	61.4	+1.5	1,477	1,453	+1.6	36.4	37.0	— 1.7
15. M. W.	10/ 8/23	♀	24	160	55.5	—0.8	1,455	1,369	+6.3	38.6	37.0	+ 4.3
15. M. W.	11/ 1/23	..	..	160	55	—1.6	1,455	1,369	+6.6	38.8	37.0	+ 4.9
16. D. K.	10/18/23	♀	22	164.5	57.8	+0.8	1,341	1,408	—4.8	34.3	37.0	— 7.3
16. D. K.	11/14/23	..	..	.....	58.2	+1.5	1,383	1,409	—1.9	35.4	37.0	— 4.4
16. D. K.	12/18/23	..	..	.....	58.0	+1.2	1,296	1,411	—8.2	33.0	37.0	—10.9
16. D. K.	12/21/23	..	..	.....	58.6	0	1,418	1,417	+0.1	36.0	37.0	— 2.8
Underweight												
17. M. A.	3/15/23	♀	25	166.2	47.3	—22.4	1,120	1,298	—13.7	30.0	37.0	—16.2
17. M. A.	4/ 9/23	..	..	166.2	47.3	—22.4	1,181	1,298	—9.0	32.6	37.0	—11.9
18. B. M.	3/26/23	♀	31	170	47.3	—27.8	1,313	1,276	+2.9	35.8	36.5	— 2.0
19. C. T.	11/19/23	♀	26	159.5	46.4	—22.5	1,415	1,274	+9.96	40.1	37.0	+ 9.7
20. B. D.	2/23/24	♀	21	159.4	41.6	—25.6	1,265	1,249	+1.3	38.2	37.0	+ 3.3
20. B. D.	3/ 4/24	♀	21	159.1	41.5	—25.6	1,172	1,248	—6.1	35.4	37.0	— 4.2
20. B. D.	3/10/24	♀	21	158.8	41.6	—25.6	1,161	1,249	—7.0	35.1	37.0	— 5.2
4. S.	2/28/24	♂	42	173.4	50.2	—30.8	1,367	1,341	+1.9	35.9	38.5	— 6.7
Overweight												
21. L.	10/22/22	♀	36	152.5	95.8	+70.1	1,896	1,687	+12.4	41.4	36.5	+13.4
22. S. T.	10/14/22	♀	17	160	91	+66.7	1,691	1,740	—2.9	36.5	40.0	— 8.7
22. S. T.	11/11/22	..	..	.....	90	+65	1,537	1,732	—11.3	33.2	40.0	—17.0
23. S. P.	2/ 5/23	♀	27	157.5	100.4	+81.1	2,168	1,783	+21.6	45.1	37.0	+21.9
24. R. K.	2/26/23	♀	26	148.5	76.4	+44.8	1,726	1,537	+12.3	42.3	37.0	+14.3
24. R. K.	5/ 8/23	..	..	.....	78.3	+49.4	1,934	1,555	+24.4	46.9	37.0	+26.7
25. M. N.	4/16/23	♀	29	155	93.6	+71.6	1,391	1,702	—18.3	30.0	37.0	—18.9
9. E. S.	4/27/23	♀	34	165	118.1	+91.2	2,546	1,931	+31.7	47.9	36.5	+31.2
9. E. S.	5/ 8/23	..	..	.....	117.8	+91.1	2,289	1,927	+18.8	43.2	36.5	+18.4
26. S. A.	5/24/23	♀	25	149.5	82.3	+55.6	1,563	1,600	—2.3	36.9	37.0	— 0.3
26. S. A.	6/ 6/23	..	..	.....	80	+51.7	1,728	1,578	+9.5	41.2	37.0	+11.4
27. G. P.	6/12/23	♀	34	163.8	101.2	+63.9	1,915	1,766	+8.4	38.8	36.5	+ 6.3
27. G. P.	7/11/23	..	..	.....	101.2	+63.9	1,664	1,766	—5.7	36.1	36.5	— 1.1
28. M. S.	6/19/23	♀	33	159.5	137.3	+136.1	2,339	2,110	+10.8	42.4	36.5	+16.4
28. M. S.	8/14/23	..	..	.....	140	+140.6	2,119	2,135	—0.7	38.4	36.5	+ 5.2
29. A. D.	7/24/23	♂	16	169.5	84.6	+37	1,929	1,969	—2.0	41.1	43.0	— 4.1
29. A. D.	7/31/23	..	..	.....	83.7	+35	1,706	1,969	—12.3	36.9	43.0	—14.2
29. A. D.	8/ 7/23	..	..	.....	82.2	+33	1,763	1,937	—8.9	38.3	43.0	—10.9
30. E. M.	8/28/23	♀	12	160.5	97.8	+92.0	1,929	1,828	+5.2	41.1	40.0	+ 2.8†
											44.7	— 8.1‡
30. E. M.	9/15/23	..	..	161.5	98.6	+90.3	2,035	1,838	+10.7	42.0	40.0	+ 5.0†
											44.7	**— 6.0‡**
30. E. M.	9/24/23	..	..	161.5	100	+92.9	1,996	1,851	+7.8	41.0	40.0	+ 2.5†
											44.7	— 8.3‡
31. R. K.	12/13/23	♀	27	149.9	75	+43	1,475	1,528	—3.5	35.9	37.0	— 3.0
32. P.	1/ 9/24	♀	32	171.1	103.1	+58	1,726	1,808	—4.5	33.5	36.5	— 8.3

* In this column, ♀ indicates female, ♂ male.
† Based on Benedict-Talbot calculations.
‡ Based on Du Bois formula.

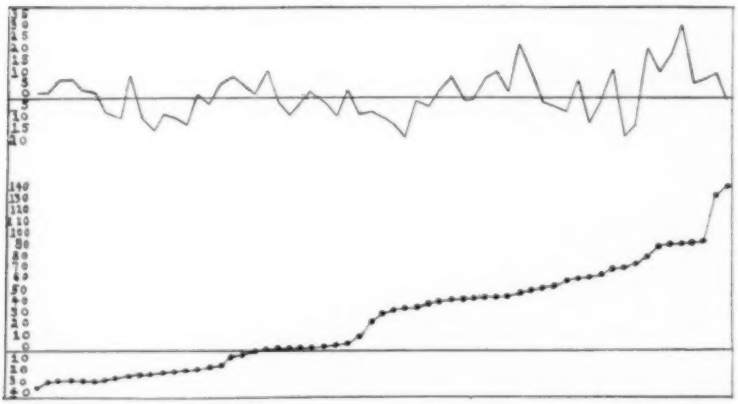
was calculated from Benedict and Talbot's studies.[16] The results are thus presented in two forms, and except in the child, aged 12 years, it

15. Carpenter, T. M.: Tables, Factors and Formulas for Computing Respiratory Exchange and Biological Transformations of Energy, Carnegie Inst. Wash. No. 303, 1921.

16. Benedict, F. G., and Talbot, F. B.: Metabolism and Growth from Birth to Puberty, Carnegie Inst. Wash. No. 302, 1921.

is quite interesting to note how closely the two methods of calculation approximate each other even with the widely varying types of persons studied.[17] Otherwise the tables require no comment.

In the chart we have drawn two curves, the lower one a weight curve showing the deviation from normal of each person, and plotted as an ascending line from the lowest weight (minus 30 per cent.) to the highest (plus 140 per cent.). In the upper curve the variation of each person from his normal basal metabolism (Harris-Benedict prediction) is correspondingly plotted. It can be seen at a glance that there is no direct or constant association between the weight variation of any one individual and his basal metabolism. All three groups show basal metabolic rates above and below the zero line, the majority being between



Results of basal metabolism experiments. Lower curve shows the deviation in weight from normal of each person. Upper curve shows the variation of each person from the normal basal metabolism.

plus and minus 10 per cent. If we pick out for study the few cases which go beyond these limits, we find that Subject 11, Table 2 (minus 18 per cent.) showed some clinical signs of myxedema. Subject 25, Table 3 (minus 18.3 per cent.) had been operated on; both ovaries had been removed.

Subject 24, Table 3 (plus 24.4 per cent.) was reciving thyroid extract at the time the test was made. On a previous occasion, she had shown a basal metabolic rate of plus 12 per cent.

Subject 23, Table 3 (plus 21.6 per cent.) was a case of subacute polyarthritis with obesity. On a previous test she had shown a basal

17. Means, J. H., and Woodwell, M. N.: Remarks on the Standards of Normal Basal Metabolism, Arch. Int. Med. **27**:608 (May) 1921.

metabolic rate of plus 12 per cent. The infection of the joints may have increased her rate.

Subject 9, Table 2 (plus 31.7 per cent. and plus 18.8 per cent.) had a large goiter, with tachycardia, nervousness and tremendous gain in weight. The thyroid gland was removed, which on section showed a colloid goiter with multiple small adenomas.

SUMMARY AND CONCLUSION

Sixty-one observations on basal metabolism were made on persons of different weight and build. These observations include eleven on six normal, seventeen on nine underweight and thirty-three on seventeen overweight subjects.

From this study it can be stated that neither excessive underweight nor excessive overweight is associated with a constant change in basal metabolism.

We therefore conclude with the statement that obesity cannot be caused by changes in the basal metabolism.

A COMPARATIVE STUDY OF THE PHENOLTETRACHLORPHTHALEIN AND HEMOCLASTIC TESTS OF LIVER FUNCTION *

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The early diagnosis of hepatic disease and of the type of lesion present is of the utmost importance. A slight enlargement of the liver with or without symptoms, or the occurrence of a group of symptoms pointing to hepatic disturbance, is not an uncommon finding. There are also some obscure abdominal conditions, in which even the diagnosis of the organ affected cannot be made conclusively. In all these cases a practical test of the liver function is a most welcome help in solving the problem.

Many clinical procedures have been described for detecting deranged hepatic function. The majority are based on one or more of the functions attributed to the organ,, but up to the present time few, if any, have been able to withstand a careful scrutiny.

In 1909, Abel and Rowntree,[1] searching for an intravenous cathartic, noticed that when phenoltetrachlorphthalein was injected into experimental animals, most of the dye was excreted by the liver and recovered in the feces unchanged. Further studies by other investigators confirmed their results, and indicated the possible value of the dye in detecting hepatic dysfunction. Considerable work was done by measuring the percentage of dye that could be recovered either from the feces or from the duodenal contents. The inaccuracy of these methods is evident, and it is due to this fault that the dye test did not receive the clinical and experimental study that it deserved.

Since Rosenthal [2] devised his new technic for the colorimetric estimation of the dye in the blood plasma, many of the errors of the older method can now be prevented. Rosenthal found that by intravenous injection of 5 mg. of phenoltetrachlorphthalein per kilogram of body weight, from 2 to 6 per cent. of the dye could be detected in the blood plasma of normal persons after fifteen minutes, and practically none at the end of one hour. In cases of liver disease, high percentages may be

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1. Abel and Rowntree: J. Pharmacol. & Exper. Therap. **1**:231, 1909.

2. Rosenthal, S. M.: A New Method of Testing Liver Function with Phenoltetrachlorphthalein, J. A. M. A. **79**:2151 (Dec. 23) 1922.

found several hours after injection of the dye. The test is one of the newest additions to our already loaded diagnostic equipment, and unless it proves of decided value it will be condemned to perish like the Cammidge and similar reactions, which are now slowly passing into the archives of medical history.

Another most interesting and promising of these new hepatic tests is founded in what Widal, Abrami and Iancovesco [3] call the "proteopexic" function of the liver. From experiments on animals with a modified Eck fistula, they found that the introduction of proteose substances into the systemic circulation so disturbed the colloidal balance of the blood, as to produce a complex reaction of constant character. They were able to duplicate their results by feeding proteins to animals with experimentally damaged livers. This indicated that the complex was dependent on the inability of the liver to perform its normal physiologic action on the digested proteins. This complex, called the "hemoclastic reaction," is manifested by a lowering of the blood pressure, hypercoagulability of the blood, decreased refractive index of the blood serum and leukopenia.

In the normal animal with intact liver, the results are correspondingly reversed, namely, rise of the blood pressure, hypocoagulability of the blood, increased refractive index of the blood serum and leukocytosis. As suggested by the authors the leukocytic factor being the most constant and easiest to determine, is the one to which especial attention should be paid. Feinblatt [4] tested eighty clinically normal medical students and in not one single instance did he fail to get a leukocytosis after ingestion of a protein. Andreen-Svedberg,[5] of Stockholm, found leukopenia to follow ingestion of protein in sixteen cases of undoubted hepatic disease. This test has been studied much more frequently in Europe than in this country. One group of investigators has suggested that it represents a vague reflex and as such has no clinical value, or that the leukopenia is only constant with "vagotonic functional neuroses". It has also been criticised in that it varies from day to day and represents merely a different distribution of the leukocytes.

In the present work a comparative study was made of the phenoltetrachlorphthalein and hemoclastic tests on cases of known or suspected liver disease. When possible, the pathologic changes of the organ were examined either at the operating table or at necropsy. A few cases of minor extrahepatic ailments were examined as controls.

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3. Widal, F.; Abrami, P., and Iancovesco, V.: Presse méd. **28**:893 (Dec. 11) 1920.

4. Feinblatt, H. M.: Alimentary Leukocytosis in Eighty Normal Men, J. A. M. A. **80**:613 (March) 1923.

5. Andreen-Svedberg, A.: Hygiea, Stockholm **85**:115 (Feb. 28) 1923.

METHODS

Phenoltetrachlorphthalein Test.—The technic of Rosenthal[2] was used, with slight modifications. A solution was made of which 1 c.c. contained 20 mg. of the dye. The patient was weighed and the calculated amount for the sterile dye (5 mg. per kilogram of body weight) was drawn into the syringe. From a vein in one arm 10 c.c. of blood was withdrawn with an appropriate needle. Through the same needle the dye was immediately injected. The need of washing the dye in with a sterile saline solution was not apparent. From a vein in the other arm, approximately 5 c.c. samples of blood were withdrawn at intervals of fifteen minutes, one hour and three hours, providing there was a retention at the end of the first hour. The bloods were centrifuged and the plasmas separated. To each was added one drop of 5 per cent. sodium hydroxid for each cubic centimeter of plasma. Assuming an alkaline solution of the dye containing 10 mg. per hundred cubic centimeters to be 100 per cent., a set of solutions was made consisting of 100, 80, 60, 40, 20 and 12 per cent. respectively. To small test tubes with equal diameters were added 0.2 c.c. portions of each of these solutions, and 0.6 c.c. of the plasma taken before the injection of the dye. This set of standards, containing respectively 25, 20, 15, 10, 5 and 3 per cent. was used in reading the unknown plasmas; 0.8 c.c. portions of the alkalinized plasmas taken after injection of the dye were placed in similar small test tubes and compared colorimetrically with the nearest standard. As a strictly quantitative method it is inaccurate, but increased accuracy would in no way enhance its value in the interpretation of liver dysfunction.

Hemoclastic Test.—The patient was fasted for at least five hours. A leukocyte count was taken. The patient drank one glass of milk and the time was noted. Four consecutive leukocyte counts were taken at half-hour intervals.

EXPERIMENTAL

Control Cases.—The six adults selected as controls were patients having medical conditions which had no apparent effect on the hepatic functions. All these cases responded to the tests within normal limits and the results are graphically represented in Chart 1, which shows the average range of variation.

CONTROL CASES

Case 1.—A man, aged 23. Chronic trachoma. The patient was otherwise healthy.

Case 2.—A man, aged 40. Tuberculosis of the cervical vertebrae. The patient was discharged improved.

Case 3.—A man, aged 28. Tonsillitis; subacute arthritis; heart normal. He was discharged cured.

CASE 4.—A man, aged 29. Acute articular rheumatism. Complete recovery.

CASE 5.—A man, aged 29. Gonorrheal ophthalmia. The patient was discharged cured.

CASE 6.—A man, aged 49. Acute empyema. Physical signs of right side empyema. Thoracotomy and drainage. The patient is improving.

Hepatic Congestion.—Passive congestion of the liver from cardic insufficiency is a common condition. Its recognition is of importance from the therapeutic standpoint, but it is a difficult task in those cases where enlargement of the organ is absent. Of course not every case of congestion shows impairment and clinically it would be very hard to diagnose. The duration of the disease and not the size of the organ is an important factor to consider. An acutely congested liver may show practically no impairment unless there is some obstruction to the outflow of bile. The hemoclastic reaction was repeated on Case 11 six months later and found to be negative.

HEPATIC CONGESTION

CASE 7.—A man, aged 32. Aortic regurgitation with decompensation. Liver slightly enlarged, not tender. Not jaundiced. The patient improved and was discharged.

CASE 8.—A man, aged 52. Mitral disease and auricular fibrillation. Liver 2½ inches (6 cm.) below costal margin. Tender to deep palpation. No jaundice. The patient was discharged in good condition.

CASE 9.—A man, aged 43. Myocardial decompensation. Liver 4 inches (10 cm.) below costal margin. Very tender. The patient became gradually worse and died soon after the test was performed. No necropsy was permitted.

CASE 10.—A man, aged 37. Mitral disease. Gigantism. Liver 3 inches (7.6 cm.) below the costal margin. Painful. No jaundice. Disease of four years' duration. The patient improved and was discharged.

CASE 11.—A man, aged 61. Chronic myocarditis. Passive congestion of the liver. Liver 4 inches (10 cm.) below the costal margin; pulsating and slightly tender liver. The liver was still enlarged and pulsating, but the physical condition was better. The patient lived six months after the test was performed.

Neoplastic Cases.—The test was applied to five cases of carcinoma and one of sarcoma. Case 12 was selected because metastatic nodules were present at a previous laparotomy. The other patients had clinical symptoms, strongly suggestive of metastases of the liver. It is important to note the large factor of safety of the organ. Only a portion of the normal liver is required to maintain the average physiologic functions of the human body. It is evident that the metastatic nodules will produce pressure necrosis on the surrounding liver cells, but unless the nodules are very numerous or very large, there will be enough healthy liver cells left to carry on the normal functions of the organ. The same explanation holds good for similar pathologic conditions like abscess or cyst of the liver.

NEOPLASMS

CASE 12.—A man, aged 61. Carcinoma of the rectum; of twenty months duration. Laparotomy two months before test disclosed metastatic nodules in the liver. The organ was not enlarged or tender. There was no jaundice. The patient was living six months after test.

CASE 13.—A man, aged 61. Carcinoma of the head of the pancreas. Bismuth series negative. Liver 2 inches (5 cm.) below the costal margin. Hard and irregular; not painful. The patient was deeply jaundiced and complained of itching. The stools were acholic. The patient died one month after the test. Necropsy showed biliary cirrhosis and the liver completely filled with metastases.

CASE 14.—A man, aged 60. Carcinoma of the stomach. The liver was not enlarged. There was no pain or jaundice. Bismuth series negative. The leukocytic test was done sixteen hours after radiotherapy. The patient died three months after the test. Necropsy showed some metastases, parenchymatous degeneration and patches of focal necrosis.

CASE 15.—A man, aged 56. Carcinoma of the rectum. Liver 1½ inches (2.30 cm.) below the costal margin. No pain or jaundice. The patient died of other causes after being discharged.

CASE 16.—A man, aged 55. Carcinoma of the colon. Diagnosis from bismuth series. The liver was negative. There was no jaundice. The patient died of pneumonia.

CASE 17.—A man, aged 23. Sarcoma of the right testicle of six months duration. The liver could not be palpated, due to a large amount of ascitic fluid. Distended abdominal veins and tenderness. No jaundice. One month after test necropsy showed sarcomatous nodules scattered through the liver.

Cholecystitis.—This group of cases comprised patients in which such diagnosis was primarily made. Of the four patients studied, three have completely recovered. Cases 19 and 21 show a normal leukocytic reaction, but with evident retention of the dye. The curves in these cases rise after the fifteen minute period. This sort of retention, also shown in Case 13, gives rise to a typical curve.

CHOLECYSTITIS

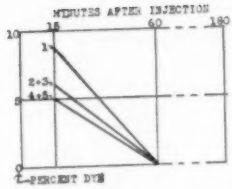
CASE 18.—A man, aged 60. Cholecystitis? Malignancy? Liver 1½ inches (2.30 cm.) below the costal margin. No pain or jaundice. The patient made rapid improvement under treatment.

CASE 19.—A man, aged 42. Acute angiocholitis. Liver 3 inches (7.6 cm.) below the costal margin. Very tender. Intense jaundice. The patient was discharged in good condition after six weeks.

CASE 20.—A woman, aged 46. Cholangitis or cholecystitis. Liver negative, grossly. The patient was jaundiced for five weeks. Operative drainage of the gallbladder with recovery.

CASE 21.—A woman, aged 52. Cholecystitis and general paresis. The patient was intensely jaundiced. The liver was not painful. Necropsy three months after the test showed the liver was larger than normal, with passive congestion.

Cirrhosis.—In this disease the fibrosis slowly impairs or destroys the hepatic cells. The greater amount of liver tissue destroyed, the greater the dye retention. The liver cells take the dye, but are sluggish in getting rid of it. Six cases of cirrhosis of the liver showed a uni-



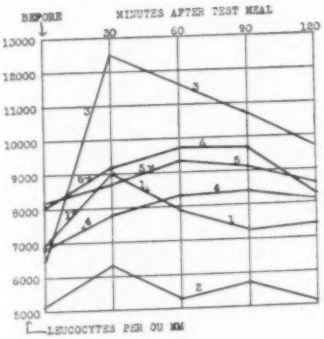
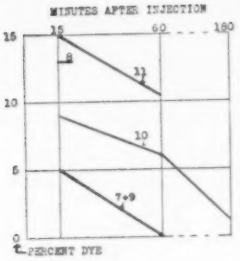


Chart 1.—Control cases.



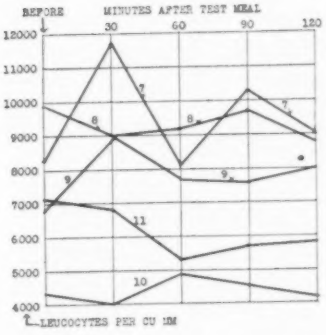
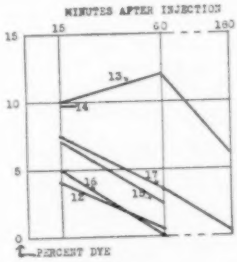


Chart 2.—Hepatic congestion.



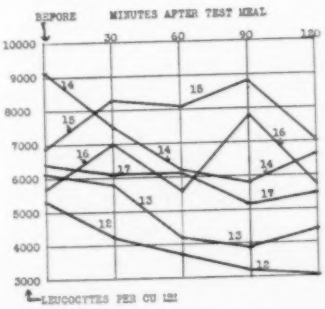
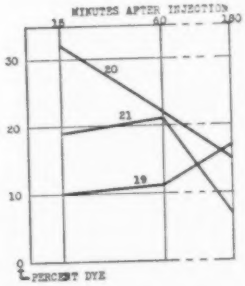


Chart 3.—Neoplasms.



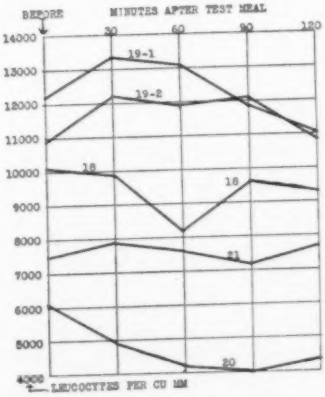


Chart 4.—Cholecystitis.

formly moderate retention. The leukocytic test showed a positive curve in all cases. Cases *23*, *24* and *27* show a delayed leukocytic reaction. The fact that these cases had ascites suggests a slow absorption of the milk as a cause of the delayed reaction.

CIRRHOSIS

CASE *22*.—A man, aged 31. Hypertrophic biliary cirrhosis of about four years' duration. Liver 4 inches (10.16 cm.) below the costal margin. Icteroid tinge. The patient left the hospital.

CASE *23*.—A man, aged 56. Atrophic cirrhosis. Ascites. Distended superficial abdominal veins. Hepatic facies. No pain or jaundice. Necropsy one

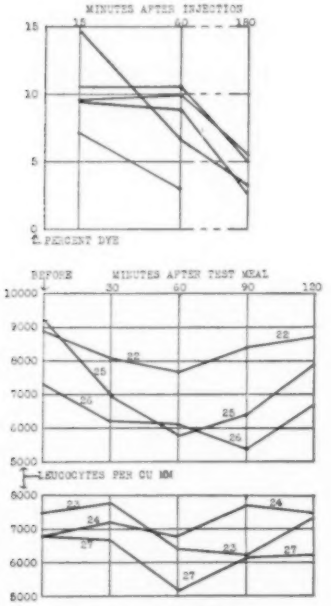


Chart 5.—Cirrhosis.

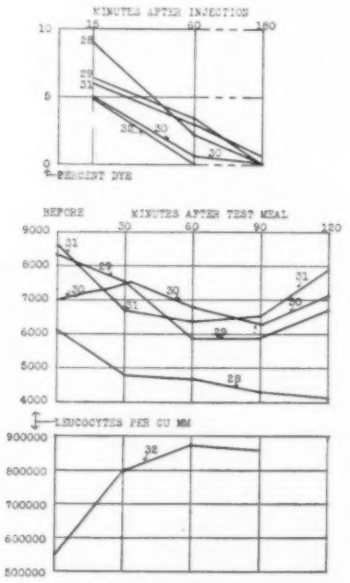


Chart 6.—Miscellaneous.

month after test showed chronic parenchymatous hepatitis; interlobular cirrhosis.

CASE *24*.—A man, aged 45. Cirrhosis of liver. Ascites. Enlarged smooth liver. Slight jaundice. No pain. Symptoms suggestive of tabes dorsalis. Necropsy disclosed that the patient died of gastric hemorrhage from varicose veins. Advanced portal cirrhosis. Miliary tuberculosis. The test was done during the hemorrhage.

CASE *25*.—A man, aged 50. Malignancy. Cirrhosis. Mass in upper abdomen, liver? No pain or jaundice. Wassermann, four plus. Necropsy two weeks after test showed ruptured thoracoabdominal aneurysm. The liver was enlarged, due to the fatty cirrhosis.

CASE *26*.—A man, aged 35. Cirrhosis with perihepatitis. The liver was 3½ inches (8.33 cm.) below the costal margin, and very tender. The spleen was

palpable. There was no jaundice. Asthenia. The history was suggestive of amebic dysentery. The patient was discharged.

CASE 27.—A man, aged 40. Cirrhosis. Pulmonary tuberculosis. The liver was 3 inches (7.6 cm.) below the costal margin, and very tender to pressure. Little ascites. No jaundice. Alcoholic history.

Miscellaneous.—In this group were included two cases of Banti's disease. Case 28 was studied before splenectomy, and Case 29 a few days after splenectomy. In this connection it is important to note the conclusion of Chaney [6] that cirrhosis of the liver indicates a bad prognosis in splenectomies. Although these cases had a positive hemoclastic, reaction, there was a small retention of dye, and both operations were followed by good recovery. Case 32 is one of lymphatic leukemia. The leukocytic counts were done with a red cell counting pipet. The results show that the large number of leukocytes did not interfere with the tests. In Case 30 the hemoclastic test was repeated six months later and found to give a positive reaction very similar to the first test.

MISCELLANEOUS

CASE 28.—A man, aged 28. Banti's disease. The liver was just palpable. The spleen large. Pronounced anemia. No ascites. No history of hemorrhage. Splenectomy with operative recovery.

CASE 29.—A youth, aged 13. Banti's disease. Very large spleen. Liver somewhat enlarged, but no gross appearance of cirrhosis at operation. Splenectomy with operative recovery.

CASE 30.—A man, aged 59. Amyloid disease of the liver. Chronic empyema. Liver 3 inches (7.6 cm.) below the costal margin. Not tender. Icteriod tinge.

CASE 31.—A man, aged 43. Chronic plumbism. Hemiplegia. Liver not enlarged. No jaundice.

CASE 32.—A man, aged 38. Lymphatic leukemia. Enlarged abdomen and liver hard to palpate. No pain or jaundice. Necropsy disclosed abdominal lymph glands, greatly enlarged. Passive congestion of an otherwise normal liver.

COMMENT

The liver may be compared to the kidney as an excretory organ. The kidney relieves the blood of its water soluble products while the liver removes those which are fat soluble. As phenolsulphonephthalein, a water soluble product, is excreted by the kidneys so phenoltetrachlorphthalein, a fat soluble substance, is excreted by the liver. Their excretion depends on the same two factors, a normal secreting cell and an open drainage. A carcinoma about the ureter or an enlarged prostate will impede kidney drainage in the same manner as angiocholitis will hinder that of the liver. There are, however, two distinct differences. First, the amount of excretory material passing through the kidney is far in excess of that passing through the liver. Second, the

6. Chaney, W. C.: Am. J. M. Sc. **165**:856 (June) 1923.

amount of secreting tissue in the liver is much more abundant than that in the kidney. The conclusion is apparent; that in the same manner as phenolsulphonephthalein gives us information as to kidney function, so should phenoltetrachlorphthalein give us corresponding data on liver function, with the important exception that the liver has a much greater factor of safety. Because of this factor of safety, one can only expect a functional test to detect a more severe dysfunction or one which involves a large number of secretory cells or the patency of the drainage system. Further study of the obscure nature of the hemoclastic test might insure a more delicate interpretation than this latter conclusion would indicate.

Examination of the charts shows a good agreement generally between the hemoclastic and phenoltetrachlorphthalein tests for liver function. There are one or two discrepancies, for which the explanation is not apparent. Some of the results would seem to indicate that the hemoclastic reaction is more sensitive than the dye test (note Cases 28, 29, 30 and 31).

Rosenthal [2] states that in early jaundice due to obstruction, before there is any extensive damage to the cells, dye is removed in practically normal time. The present data do not agree with this statement, but show that there is retention due apparently to the mechanical obstruction, and under these circumstances the hemoclastic reaction is negative (note Case 19 of acute angiocholitis). It is suggested that the leukocytic test measures directly the physiologic integrity of the liver cells, while the dye test measures this integrity dependent on the patency of the biliary drainage system.

As shown by the charts, there may be more dye in the blood stream at the end of one of three hours than there is at the end of fifteen minutes, producing a distinctly typical curve. It is possible that there is a reabsorption of the dye from the bile capillaries by the lymphatics of the liver, in a manner similar to that by which bile itself enters the circulation in cases of jaundice.

The uniformity of the results in cirrhosis is quite striking. The retention is not especially marked and definitely persists at the end of three hours. It emphasizes again the reliability of the liver function tests, when all or a majority of the cells are involved, in contrast to neoplastic metastases where only a portion of the cells are concerned.

The marked leukocytosis in some of the normal cases would cause one to believe that more emphasis should be laid on the relation of diet to the time at which routine leukocyte counts are made in many hospital laboratories.

Localized phlebitis occasionally follows injection of the dye. It is transient and of no consequence. A few patients complained of slight epigastric distress. Catharsis was produced in three cases.

SUMMARY

1. The hemoclastic and phenoltetrachlorphthalein tests of liver function are used in groups of cases with primary or secondary liver disease. The comparative results of tests are presented, with short comments on each group of cases tested. In many cases the pathologic changes of the organ were determined either at operation or at necropsy.

2. It is suggested that the hemoclastic reaction measures directly the physiologic capacity of liver cells, while the dye test measures this capacity dependent on the patency of the biliary passages.

3. The hemoclastic reaction appears to be more sensitive than the dye test, but a combination of the two is often helpful in diagnosis or even prognosis of obscure hepatic disease.

4. Emphasis is laid on the large factor of safety of the liver, which precludes the use of any functional test to detect minor disturbances of the organ.

HEMOCHROMATOSIS WITH SPECIAL REFERENCE TO ITS FREQUENCY AND TO ITS OCCURRENCE IN WOMEN *

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INTRODUCTION

During one year, from March 1, 1922, to March 1, 1923, ten cases of hemochromatosis came to necropsy in the Pathological Department of the Boston City Hospital, and of these ten, two occurred in women. Another case occurring in a neighboring hospital during this same period was put at our disposal. On going back over the records of the department for the previous twenty-four years, six additional cases were found of which one was a woman.

The rarity of the disease not only clinically but also as a postmortem finding has always been emphasized, and the small number of cases recorded in the literature (less than one hundred) bears this out. Its occurrence in women has frequently been doubted and even denied because only one accepted case has so far appeared in print.

An analysis and discussion of these seventeen new cases, chiefly from the clinical point of view, seems advisable because they present interesting deviations from the textbook picture. In addition, on account of the rarity of female cases their clinical and postmortem records, so far as obtainable, are presented in detail. The literature will be referred to only when necessary.

The clinical observations available are not so complete as could be desired for the following reason. Hemochromatosis can be diagnosed clinically only in its late stages when the clinical syndrome, namely, the signs and symptoms pointing to cirrhosis of the liver, pigmentation of the skin and diabetes are all present. Pathologically, all stages of the disease, from its early beginnings, can be recognized, and on this account a postmortem diagnosis is comparatively simple. In this series of seventeen pathologically advanced cases, all with well marked pigment cirrhosis, only two were recognized during life and proved positive by the demonstration of hemosiderin in an excised bit of skin. Most of the patients died of intercurrent affections, such as lobar pneumonia, meningitis, etc., and a detailed clinical history was often not obtainable. The pathologic diagnosis in all instances was based on the presence of the two pigments characteristic of hemochromatosis, namely, hemofuscin and hemosiderin, in the cirrhotic liver and also in the pancreas and various other organs and tissues.

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* From the Pathological Laboratory of the Boston City Hospital.

Study of the islands of regeneration [1] in the human cases of pigment cirrhosis shows that the young liver cells are at first nonpigmented, then granules of hemofuscin accumulate in them and in the course of time are transformed into hemosiderin.

FREQUENCY OF OCCURRENCE

Although occurring quite universally (in China, Japan, Germany, France especially perhaps, England, the United States) hemochromatosis is, as already stated, considered a rare disease. On this account the following statistics from the Pathological Department of the Boston City Hospital, covering a period of twenty-six years, from January 1, 1897 to March 11, 1923, are of interest:

Necropsies on adults, 3,760; number of cases of hemochromatosis, 16; percentage of cases of hemochromatosis, 0.42.

There are three other well marked cases which cannot be included in this series because they are complicated by the presence of alcoholic hyalin, and it seems best to confine this study to the pure pigment type of lesion.

The statistics for the one year, which includes the ten cases, necessarily gives a much higher percentage, a figure which has probably never been reached before:

Necropsies of adults, 289; number of cases of hemochromatosis, 10; percentage of cases of hemochromatosis, 3.46.

No explanation of this high percentage is evident, for during the succeeding year under exactly the same conditions and with interest unabated, not a single case has been seen. The large number of cases must probably be considered an accidental occurrence.

CAUSE

Recently [1] it has been shown that it is possible to produce pigment cirrhosis in rabbits by means of chronic poisoning with copper salts, and that the lesion similar to that in hemochromatosis is characterized by the deposition of hemofuscin in the liver and other cells. In the course of time this pigment very slowly changes to hemosiderin.

In studying the clinical records of our cases, particular attention has been paid to the possibility of poisoning by copper. The results obtained are strongly suggestive but not convincing. The two most likely sources are an occupation which exposes a person to the inhalation and swallowing of copper dust, and excessive indulgence in distilled liquors.

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1. Mallory, F. B.; Parker, Frederic, Jr., and Nye, Robert N.: J. M. Res. **42**:461, 1921.

The patient (Case 8) from the Peter Bent Brigham Hospital [2] had worked for twelve years in a shop "milling and turning copper and brass." The body presented the typical picture of the disease which was recognized and proved during life. Another patient not included in this series, because the lesion was not advanced enough, had worked for six years in a brass foundry and then on account of "brass colic" changed to an iron foundry for the ten years preceding his death. While the liver showed but little hemosiderin the stroma around the blood vessels and in the capsule contained relatively large amounts of hemofuscin. Evidently the hemofuscin in the liver cells had changed to hemosiderin and had been for the most part gradually removed, but in the connective tissue cells this change had not occurred and therefore the hemofuscin, not being soluble, had persisted.

Four other patients in our series had been metal workers and exposed to copper for many years; one spent two years milling and planing brass and then had continued for thirty-six years in the same poorly ventilated, dusty quarters working on high grade steel; another forged metals for twenty-five years in a railroad shop where copper was handled; one was a lineman for a fire department for twenty-three years, fixing cable and telegraph wires; still another worked for thirteen years in a factory polishing pipe wrenches in the same quarters where brass pipes were milled and worked.

In six of our cases a history of marked or excessive use of alcohol was obtained. In three it was denied, in two no history was available. An alcoholic history is of significance because distilled liquors frequently contain copper, often from a trace to 10 mg. to the liter, but occasionally in considerable quantity. In one sample, analyzed by Dr. L. T. Fairhall,[3] there were 185 mg. of copper to the liter. The source of the copper in distilled liquors is probably to be found in the action of volatile acids, especially acetic, passing over with the alcohol and acting on the copper coil of the distilling apparatus.

Other possible sources of copper are "coppered" peas, beans and pickles, apple butter which is acid and usually cooked in copper kettles, and perhaps copper utensils (kettles, saucepans, hot water heaters, etc.). One patient had worked for eighteen years in a cannery cooking fruits in copper kettles. In a small proportion of our cases, less than a third, no source of copper poisoning was evident.

AGE

Hemochromatosis does not occur in children. Sprunt [4] states that the disease period is from 30 to 70 years of age but no patient under

2. We are indebted to Dr. G. H. Hansmann for the necropsy material and to Dr. H. A. Christian for the clinical history.

3. Personal communication to Dr. F. B. Mallory.

4. Sprunt, T. P.: Hemochromatosis, Arch. Int. Med. **8**:75 (July) 1911; Nelson Loose-Leaf Living Medicine **3**:207, 1920.

34 was found in the literature. In our series the youngest and incidentally one of the most marked cases was in a woman, aged 31, while the oldest was in a man, aged 84. The advanced age at which the disease makes itself evident clinically is a strong argument in favor of the view that the lesion is exceedingly chronic and requires a minimum of ten years in which to develop. The fact that youth is not affected suggests that it is not exposed to the toxic agent which causes the disease.

SEX

Women are usually considered immune to hemochromatosis because, as already stated, only one generally accepted case [5] is on record. The addition of these new cases, all well marked and proved by postmortem examination, must necessarily change this point of view. Evidently the disease is rare in women not on account of any immunity but owing to less exposure to the sources of poisoning which could cause the lesions. We have found the earlier stages of the process in the liver in several other women, sometimes alone, sometimes associated with alcoholic cirrhosis.

SIGNS AND SYMPTOMS

The order of occurrence of the lesions of hemochromatosis, which produce the syndrome characteristic of the disease, are cirrhosis of the liver, pigmentation of the skin and sclerosis of the pancreas. Eleven of our series were admitted with signs and symptoms directly referable to one or all of these lesions. The remaining six entered the hospital because of complications (lobar pneumonia, meningitis, etc.). Eight complained of swelling of the abdomen and of symptoms arising therefrom, and five of jaundice. Three had noticed gradual darkening of the skin of the face, neck and arms. A majority when questioned admitted asthenia, loss of weight, and absence of the usual well being. Only one had intermittent dull aching pain in the region of the liver. One was found dead in bed and no cause of death other than the cirrhosis was discovered. One showed the usual train of diabetic symptoms, polyuria, polydipsia and polyphagia. In other words, ten had signs or symptoms pointing to the cirrhosis, three to involvement of the skin and only one to diabetes. The liver was not found to be constantly large. Indeed in most cases it was of small size or within the normal limits. It was not grossly distorted in shape unless complicated by some other condition and the surface was finely nodular, in a number of instances of a "pebble-leather" character, differing from the alcoholic hobnail type. The variations in size of the liver were found to have a very definite relation to the presence of symptoms indicative of obstruction to the flow of blood or bile. When the organ was large

5. Abbott, Maude E.: J. Path. & Bacteriol. **7**:55, 1901.

gastro-intestinal disturbances, abdominal varicosities, ascites and jaundice did not as a rule occur. On the other hand when it was small one or all of these were common. The table shows the weight of the liver and its relation to obstructive symptoms. When its weight was above 1,800 gm. (upper normal limit) ascites and jaundice were not present except in two instances as a terminal event. When below this, either persistent jaundice or ascites was almost constant. Of seventeen cases, nine were jaundiced, two, however, only just before death. In two the duration of the icterus exceeded six months. In eight there was ascites and in six the two symptoms were combined. In one there was jaundice, but no ascites owing to well marked compensatory circulation.

The size of the liver probably depends on one or all of several factors, such as the stage of the process, the quantity of toxic agent ingested and the amount of inflammatory reaction to the injury pro-

The Weight of the Liver and Its Relation to Obstructive Symptoms

Case	Weight of Liver, Gm.	Weight of Spleen, Gm.	Evidence of Obstruction in Liver
1	5,400	240	None (primary cancer of liver)
2	3,280	...	None
3	2,930	405	Jaundice (terminal)
4	2,500	150	None
5	2,215	Small	None
6	2,185	200	None
7	2,015	440	Jaundice (terminal)
8	1,915	180	Ascites (trace)
9	1,900	560	Ascites and jaundice (primary cancer of liver)
10	1,840	230	None
11	1,400	350	Ascites and jaundice
12	1,270	168	Ascites and jaundice
13	1,260	180	Ascites and jaundice
14	1,200	400	Jaundice (well marked compensatory circulation)
15	1,100	290	Ascites
16	1,024	390	Ascites and jaundice
17	Large	250±	Ascites and jaundice (primary cancer of the liver)

duced by it, the presence or absence of regeneration, and rarely fatty infiltration. Probably the time factor is important. In the early stages, necrosis, inflammatory reaction, and regeneration lead to enlargement of the organ. Later, when regeneration plays a less important part and the increased stroma contracts, the organ diminishes in size. If the process is very slow, the circulation of the blood and the flow of the bile may accommodate themselves to the condition so that obstruction of either does not occur. If, however, the changes are more rapid, blocking of the blood and bile may result and ascites and jaundice take place. As a result of the liver lesion death may occur before the other signs of the syndrome have had time to develop.

The size of the spleen (see table) bears no relation to the size of the liver. It was by no means constantly large, for in five cases it was below 200 gm. These particular findings as regards the liver and spleen are of special interest because they vary widely from what has been described. Thus Sprunt,[4] in summing up the literature, says in part:

"The liver is characteristically large and irregular, and may be tender. The spleen is also enlarged and as a rule is easily palpable. There is no jaundice."

Pigmentation of the skin, the second of the classical signs, usually precedes the diabetes and is of two distinct types.[1] The characteristic type is due to the presence of the hematogenous pigments, hemofuscin and hemosiderin in the corium, especially around the coil glands, but also in the subcutaneous fat tissue. It shows itself as a dull gray-brown or dirty brown discoloration of the skin of the extremities (face, neck, forearms, hands, front of wrists, legs). A positive diagnosis of hemochromatosis during life is based on the demonstration of the presence of hemosiderin in an excised piece of skin.

The other type of pigmentation is due to increase of melanin in the skin and other organs and tissues of the body in places where it normally occurs, and is without much question due to injury of the adrenal glands by the accumulation of the hemotogenous pigments there. In other words, Addison's disease is produced. As the lesion in the adrenals is confined practically to the zone glomerulosa it would seem as though destruction of this layer was chiefly responsible for the increase of the melanin.

The two types of pigmentation ordinarily occur separately but may and do occur together, and this probably accounts for the variations in the descriptions of the appearance of the skin in hemochromatosis by different authors.

Diabetes mellitus is always a late symptom when due to the pigmentation, necrosis and sclerosis of the pancreas, but hemochromatosis may of course complicate diabetes that is already existing. One of the two cases in our series had been a mild diabetic patient for years. In the other, diabetes followed pigmentation of the skin and ran a rapid and progressive course to a fatal termination.

Complications of the disease are of frequent occurrence, as with any other very chronic disorder but it has one sequela, primary liver cell carcinoma, which is relatively frequent and which it shares with the other chronic lesion of the liver, namely, alcoholic cirrhosis. In our series of seventeen cases we had three well marked examples. The lesion evidently arises as a result of the continued necrosis and regeneration of liver cells. Some one cell eventually gets beyond normal control and proceeds to proliferate with the resulting formation of a carcinoma. Whenever the liver is unusually large, and particularly when the increase in size is not uniform, superimposed malignancy should be suspected. In Case 1 the right lobe was found to be almost entirely replaced by tumor, and the hepatic vein and inferior vena cava almost completely occluded by a cancerous thrombus without, however, at any time causing obstruction to the flow of blood or bile.

Besides the one generally accepted case[5] two others have been claimed but never proved. This one case had a strong alcoholic history.

In our series the first patient of the three cases occurring in women also had an alcoholic history. Little else is known because she was found dead in bed. Necropsy showed a large liver and intense generalized pigmentation, with a slight amount of iron pigment in the skin but no ascites or jaundice. The other two cases gave no history of alcoholism, both were jaundiced and one had ascites. The livers were small.

REPORT OF CASES

CASE 1.—C. H., a woman, aged 31, was found dead in bed, July 30, 1902. A long history of alcoholism was obtained.

The necropsy showed a well developed, fairly well nourished, white woman. No marks of violence were present. Pigmentation of the skin was not obvious. The myocardium was a dark reddish brown, otherwise the heart was negative. The lungs and spleen were grossly negative. The pancreas was a dark chocolate brown color. The liver weighed 2,500 gm. Its surface was dark brown and finely nodular. The consistency was definitely increased. On section, the cut surface was brown with fine interlacing slightly depressed darker chocolate brown strands of tissue which divided it off into islands, varying up to 3 mm. in diameter. The kidneys were not grossly remarkable. The adrenals showed a dark brown line just beneath the capsule. The endometrium was characterized by a similar but fainter brown tint. In gross, the Prussian blue reaction was intense in the liver, heart, pancreas, cortex of adrenal, stomach, douodenum, and less marked in the kidneys, ovaries, spleen and cervical mucous membrane.

Microscopically, the heart muscle, pancreas, liver, kidney, mucosa of stomach and duodenum, and retroperitoneal lymph nodes showed hemosiderin and hemofuscin in characteristic locations. The liver showed an increase in the periportal connective tissue, which was diffusely infiltrated by endothelial leukocytes engorged with hemosiderin. In many places, especially about vessels, the fibroblasts themselves contained hemofuscin and hemosiderin. The liver cells throughout were loaded with hemosiderin. Here and there small islands of these showed only small amounts of hemosiderin and hemofuscin. No alcoholic hyalin was present. Traces of hemosiderin were present about the coil glands of the skin.

CASE 2.—N. K., a woman, aged 65, was admitted to hospital, Nov. 16, 1922, and died nine days later. Her complaints were swelling of the abdomen and jaundice.

Past History.—The patient's habits were good. No alcohol. She lived an easy life with her daughter, and was always healthy with one exception until onset of present illness; five years ago she had an attack of jaundice which cleared up without treatment in six weeks.

Present Illness.—Began seven weeks before death with insidious onset of jaundice. The abdomen also began to swell and a physician was called. Fluid was drawn off but soon recurred. Jaundice persisted and the abdomen was tapped many times before admission. During this time patient was not ill enough to be confined to bed.

Present Examination.—An emaciated white woman was seen moaning in bed. The sclerae were slightly jaundiced. The heart and lungs were normal. The abdomen was distended by fluid and gas. There was shifting dulness in the flanks, and slight edema of the ankles. Otherwise there was nothing worthy of note.

November 22, the abdomen was tapped. From 10 to 11 liters of straw colored fluid was withdrawn. The edge of the liver was felt. The patient died some hours later.

Necropsy revealed a poorly developed and poorly nourished white woman. The sclerae were jaundiced. Edema of the legs was present. The skin was yellow-gray with brown spots resembling freckles on the arms and legs. There was a fluid wave in the abdomen. In the peritoneal cavity was 1,500 c.c. of dark, amber colored fluid. There were adhesions in the region of the gallbladder. The mesenteric and retroperitoneal lymph nodes were enlarged and dark colored. Prussian blue reaction was marked. The pleural and pericardial cavities were normal. The heart, lungs, spleen, kidney and adrenals were essentially negative. The liver weighed 1,260 gm. Its surface was grayish-brown, finely nodular, hard, tough and leathery. The cut surface was deep brown with fine brownish-green slightly depressed strands traversing it. Aorta showed generalized sclerosis with calcification. Prussian blue reaction was marked in the liver, lymph nodes and spleen.

Microscopically, the liver showed moderate increase in periportal fibrous tissue. Many of the fibroblasts were loaded with hemofuscin, especially about the arteries. This fibrous tissue was infiltrated by endothelial leukocytes engorged with hemosiderin. The liver cells were filled with hemosiderin. The islands of regeneration showed both pigments. The retroperitoneal lymph nodes and spleen were infiltrated by endothelial leukocytes engorged with hemosiderin. Fibroblasts of the stroma contained both pigments in moderate amounts.

CASE 3.—E. D. B., a woman, aged 60, who showed at necropsy marked dilatation of the veins of the abdominal wall and of the esophageal plexus, a small (1,200 gm.) nodular cirrhotic liver, a large spleen and jaundice. Microscopically, no alcoholic hyalin could be found in the liver. Hemosiderin and hemofuscin were present in liver and pancreas, in characteristic distribution. The spleen was negative but convoluted tubules of the kidney showed much hemosiderin.

SUMMARY

This paper presents an analysis of seventeen cases of hemochromatosis, which with one exception came to necropsy at the Boston City Hospital during the last twenty-six years. Fourteen cases were patients in the wards, and ten, or 62 per cent. came to necropsy during one year (1922-1923).

The series includes three women.

Five patients in their occupations had had long exposure to copper, and at least six cases had a strong alcoholic history.

Six patients were admitted with symptoms directly referable to the disease. Eight complained of swelling of the abdomen or symptoms therefrom, and five of jaundice. Three had noticed gradual darkening of the skin of the face, neck and arms. One patient was found dead in bed, and no cause of death other than the hemochromatosis was discovered. Six patients were admitted, and died because of associated but irrelevant lesions. Three died of superimposed primary liver cell carcinoma.

The spleen varied in size from large to small, and the variations were not related to the size of the liver.

Skin pigmentation is of two types, one due to hematogenous pigments, the other to melanin.

Hemochromatosis may be complicated by alcoholic cirrhosis and vice versa.

CONCLUSIONS

Chronic poisoning with copper may be the cause of hemochromatosis. The most likely sources of the copper are occupations involving exposure to copper and brass, excessive indulgence in distilled liquors, and possibly "coppered" food stuffs.

The liver is not constantly large, it may be small but is often of normal size.

The spleen may be large or small.

Ascites and jaundice both occur. Their frequency bears a definite relation to the size of the liver.

The disease occurs in females.

Primary liver cell carcinoma is a not infrequent sequela.

A CLINICAL STUDY OF BLOOD FIBRIN

WITH OBSERVATIONS IN NORMAL PERSONS, PREGNANT WOMEN, AND IN PNEUMONIA AND LIVER DISEASE *

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INTRODUCTION

Foster and Whipple [1] have reported a method for the quantitative analysis of blood fibrin which is suitable for clinical investigation because it is relatively accurate, and requires but 5 c.c. of blood on analysis. Their work demonstrated that small variations in the level of blood fibrin occur in normal dogs while disease (experimentally produced) in these animals causes very wide and rapid fluctuations of this blood protein.

Injury to any tissue, excepting the liver, was found to cause an increase in the blood fibrin content. This increase was constantly observed, for example, when sterile abscesses were produced by the subcutaneous injection of turpentine, when the animal was exposed to massive doses of deep roentgen rays or when suffering from "distemper," a common acute respiratory infection in dogs. If the liver is severely injured, as by chloroform or phosphorus, a decrease and not an increase in blood fibrin occurs. However, following mild as opposed to severe liver injury, there tends to be a rise instead of a fall. These observations on animals led to the clinical investigation reported in the present communication.

Older methods of fibrin and fibrinogen analysis have been discussed and compared with the method used here, in the work by Foster and Whipple.[1] Cullen and Van Slyke [2] in 1920 and Gram [3] in 1921 have reported methods of analysis which give results similar to those obtained in the present work.

NORMAL FIBRIN VALUES

The most extensive series of fibrin determinations in health and disease yet published is that by Gram.[4] His figures for the normal

* From the Medical Laboratories of the Massachusetts General Hospital.
* This paper is No. 35 of a series of papers on the physiology and pathology of the blood, from the Harvard Medical School and allied hospitals, a part of the expense of which has been defrayed by a grant from the Proctor Fund for the study of chronic disease.

1. Foster, D. P., and Whipple, G. H.: Am. J. Physiol. **58**:365 (Jan.) 1922.
2. Cullen, G. E., and Van Slyke, D. D.: J. Biol. Chem. **41**:587 (April) 1920.
3. Gram, H. C.: J. Biol. Chem. **49**:279 (Dec.) 1921.
4. Gram, H. C.: Acta Med. Scandinav. **56**:107 (March) 1922 (article in English).

fibrin are based on twenty-five analyses on men and the same number on women. His average results and those of other investigators are compared with mine in Table 1. The average figures presented in this paper are based on duplicate analyses on twenty-three normal men and nineteen normal women.

The results reported by Hammarsten [5] and Mathews [6] are based on a small number of analyses and were computed before the more accurate methods were devised. Their figures are, therefore, probably less accurate than those of later workers. Whipple's [7] figures are styled by him as "normal or approximately normal." He has included cases which show results we now know to be abnormal.

TABLE 1.—*Fibrin Determinations in Normal Persons Taken from the Literature*

Investigator		Men		Women		Men and Women,
		Fibrin per 100 C.c. Plasma	Fibrin per 100 C.c. Blood	Fibrin per 100 C.c. Plasma	Fibrin per 100 C.c. Blood	Fibrin per 100 C.c. Plasma
Hammarsten	Maximum	...	...	...	...	650
	Minimum	...	...	...	...	101
	Average	...	...	...	...	420
Mathews	Maximum	...	...	...	...	600
	Minimum	...	...	...	...	150
	Average	...	...	...	...	375
Whipple, 7 determinations	Maximum	...	...	...	...	591
	Minimum	...	...	...	...	385
	Average	...	...	...	...	506
Foster and Whipple, 4 determinations	Maximum	364	178	...	...	...
	Minimum	316	163	...	...	...
	Average	335	172	...	...	...
Gram, 50 determinations	Maximum	360	190	380	210	...
	Minimum	200	110	210	120	...
	Average	270	140	290	170	...
Foster, 42 determinations	Maximum	446	210	470	233	...
	Minimum	256	112	255	143	...
	Average	332	163	344	179	...

Table 2 gives in detail the results of the fibrin analyses, from which the average figures recorded in Table 1 for the present work were computed.

The data in Table 3 is presented primarily to emphasize the fact that the extremes of normal fibrin values recorded are rarely reached, the vast majority of results falling within the limits for men of from 250 to 400 mg. per hundred cubic centimeters of plasma or from 125 to 200 mg. per hundred cubic centimeters of blood. The extreme values reported by Mathews,[6] Hammarsten [5] and Whipple [7] were not observed.

5. Hammarsten, Olof: A Text Book of Physiological Chemistry, New York, John Wiley & Sons, 1914.

6. Mathews, A. P.: Physiological Chemistry, New York, William Wood & Co., 1920.

7. Whipple, George H.: Am. J. Physiol. **33**:50, 1914.

The figures for women show a similar variation, but are slightly higher, being from 300 to 425 mg. per hundred cubic centimeters of plasma or from 150 to 225 mg. per hundred cubic centimeters of blood. It seems

TABLE 2.—*Normal Fibrin Values*

Men							Women						
				Fibrin							Fibrin		
Age	Temperature, F.	Pulse Rate per Min.	Hematocrit, per Cent. Red Blood Cells	Average Two Determinations, Mg.	100 C.c. Plasma, Mg.	100 C.c. Blood, Mg.	Age	Temperature, F.	Pulse Rate per Min.	Hematocrit per Cent. Red Blood Cells	Average, Two Determinations, Mg.	100 C.c. Plasma, Mg.	100 C.c. Blood, Mg.
22	98	66	48	4.65	296	153	22	....	..	56	5.45	353	155
30	97.6	80	54.5	7.3	405	184	24	....	..	47	5.0	304	161
28	97.6	72	54.0	6.15	390	178	43	....	..	48	6.0	373	194
25	97.6	64	38	5.65	287	178	52	....	..	44	6.15	374	210
39	99	78	54	5.7	354	165	35	98.6	78	44.5	5.05	306	167
45	98.2	72	56	4.05	256	112	21	98.6	80	44	4.2	255	143
49	98	60	51	4.2	264	129	25	98	78	46.5	5.3	320	171
27	98.6	70	57	5.25	342	147	21	98.6	82	46	5.2	321	173
61	98	80	50	4.85	287	143	21	98	76	44	5.4	323	181
57	....	..	53	7.0	446	210	26	....	..	42	5.0	298	173
63	....	..	49	6.0	372	190	16	....	..	48	5.45	342	178
48	....	..	49.5	6.35	390	196	24	....	..	44	5.2	314	176
22	....	..	54.5	5.4	340	155	45	98.6	78	51	7.3	475	232
11	....	..	43.5	6.1	370	198	58	98	82	46.5	6.2	378	202
28	....	..	54.5	5.0	320	145	28	98.6	80	45.0	6.1	371	204
24	....	..	49	5.0	322	164	33	98.6	90	47.5	5.5	342	180
27	98	72	49.5	5.0	310	156	53	99	90	43.5	6.3	382	216
40	....	82	51	6.05	382	187	63	98.6	88	47.6	6.55	400	209
3	98.2	82	51	4.9	305	150	27	99	88	50.6	6.65	411	203
23	99	80	52	4.65	292	139							
50	....	..	52.5	6.1	339	161							
28	98	70	51.6	6.3	388	187							
55	....	..	44.6	4.85	305	169							
Averages.....			49	....	332	163	.....			46	....	344	179
Highest.....			57	....	446	210	.....			56	....	475	233
Lowest.....			38	....	256	112	.....			42	....	255	143
Difference between highest and lowest.....			15	....	190	98	.....			14	....	220	90

TABLE 3.—*Distribution of Fibrin Values in Normal Men and Women*

Men				Women			
Fibrin per 100 C.c. Plasma, Mg.	Number of Cases	Fibrin per 100 C.c. Blood, Mg.	Number of Cases	Fibrin per 100 C.c. Plasma, Mg.	Number of Cases	Fibrin per 100 C.c. Blood, Mg.	Number of Cases
450 and above	0	225 and above	0	475 and above	1	250 and above	0
425 to 449	1	200 to 224	1	450 to 474	0	225 to 249	1
400 to 424	1	175 to 199	9	425 to 449	1	200 to 224	8
375 to 399	4	150 to 175	7	400 to 424	3	175 to 199	5
350 to 374	3	125 to 149	5	375 to 399	2	150 to 174	6
325 to 349	3	100 to 124	1	350 to 374	4	125 to 149	1
275 to 299	4	.....	...	300 to 324	6	.....	...
250 to 274	2	.....	...	275 to 299	1	.....	...
.....	...	.....	...	250 to 274	1	.....	...
300 to 324	5	.....	...	325 to 349	2	100 to 124	0

possible that the extreme values recorded may be due to some clinically unrecognized pathologic conditions. That there is a normal variation in fibrin values seems to be established by Gram's work and by that of Foster and Whipple on dogs as well as by the data offered here.

FIBRIN VALUES IN NORMAL PREGNANCY

Before undertaking the study of fibrin in the toxemias of pregnancy, ten estimations were made on normal pregnant women to ascertain the physiologic variation in this state. Gram [4] found that as pregnancy progresses, the blood fibrin level rises. This observation was confirmed by the present work. The patients examined were in from the sixth to the eighth months of pregnancy and were clinically free from disease. Table 4, in which the results of these determinations are given, shows the average fibrin value for the plasma to be 415 mg. per hundred cubic centimeters in pregnant women as compared with 344 mg. per hundred cubic centimeters in the nonpregnant. The average value for the whole blood was found to be approximately 94 mg. higher in pregnancy.

TABLE 4.—*Fibrin Values in Normal Pregnant Women* *

Month of Pregnancy	Systolic Blood Pressure	Hematocrit, per Cent. Red Blood Cells	Fibrin: Average Two Determinations, Mg.	Fibrin: 100 C.c. Plasma, Mg.	Fibrin: 100 C.c. Blood, Mg.	Remarks
6	125	37	5.8	346	218	Slight edema of legs
8	120	43	9.0	540	308	Constant leukorrhea
8	120	37	6.6	391	246	
8	100	46	7.6	473	255	
8	105	39	7.2	430	262	
8	130	38	8.0	475	295	
7	110	38	6.6	402	250	
8	110	42	8.4	505	294	
8	115	38	9.8	592	330	Slight trace of albumin in urine
9	110	39.6	7.6	455	275	
Averages		38.9	...	414.9	273.3	
Highest		46.0	...	540	330	
Lowest		37.0	...	346	218	
Difference between highest and lowest		9.0	...	194	112	

* The temperature of these women was normal.

FIBRIN VALUES IN TOXEMIA OF PREGNANCY

In view of the foregoing experiments on dogs with liver necrosis [1] it was anticipated that patients suffering from toxemia of pregnancy might show a pathologic fibrin curve, because these patients at necropsy typically show some degree of liver necrosis. It was found that toxemia suscepts fell into two groups: (1) patients with nephritis and (2) patients without nephritis. Blood pressure readings and the albumin examinations of the urine are included in the tables, as they are the most reliable clinical data suggesting the onset of toxemia. Whether a patient had chronic nephritis or not was finally determined by examination several months postpartum for clinical and laboratory evidence of this disease. In this series of six cases, with symptoms suggesting toxemia (headache, lassitude, loss of appetite, elevated blood pressure,

together with edema and albuminuria), those demonstrated to have nephritis showed a normal or but slightly elevated blood fibrin, while the cases of eclampsia and preeclamptic toxemia tended to show a more marked elevation of the blood fibrin level. In neither group did the fibrin values become subnormal, and none of the cases studied were fatal. Only one of the typical cases of toxemia had convulsions, and

TABLE 5.—*Fibrin Values in Four Cases of Toxemia of Pregnancy*

Date	Blood Pressure: Systolic	Blood Pressure: Diastolic	Hematocrit Red Blood Cells, per Cent.	Fibrin: Average Two Determinations, Mg.	Fibrin: 100 C.c. Plasma, Mg.	Fibrin: 100 C.c. Blood, Mg.	Remarks
Mrs. H.	Mild toxemic symptoms.			No convulsions.			
7/ 1	140	100	39.0	8.0	486	297	Urine, very slight trace albumin
7/ 2	140	100	39.5	8.4	492	298	Symptomless
7/ 3	150	100	39.5	8.0	475	286	
7/ 5	159	112	44.5	8.6	510	280	Edema of hands; urine, slight trace albumin, headache
7/ 7	160	120	41.8	7.3	440	256	
7/ 8	...	...	....	....	...	...	Delivered (low forceps)
7/11	130	100	39.0	10.1	580	354	
7/15	130	90	38.0	8.2	485	292	Normal convalescence; urine, very slight trace albumin
Mrs. B.	Moderately severe toxemia.			No convulsions.			
6/23	180	?	90	....	...	...	Bled, 250 c.c.
6/29	130	80	33	10.2	566	400	Urine, slightest possible trace albumin; clinically toxic
7/ 1	140	90	32.6	9.9	576	389	
7/ 3	140	90	27.0	8.2	470	344	Clinically improved
7/ 4	...	...	....	....	...	...	Discharged, home
7/ 7	120	80	26.4	8.4	478	351	Nonprotein nitrogen (blood), 34.8 mg. per 100 c.c.
7/ 8	130	90	28.0	7.9	450	324	
7/26	...	...	....	....	...	...	Delivered of twins
7/29	130	90	29	9.4	500	416	This rise is probably due to the repair of uterine trauma of birth, and is normal and regularly seen
Mrs. Mc.	Severe toxemia.			No convulsions.			
7/13	140	100	44	10.4	632	355	Slight trace albumin in urine
7/17	150	100	48	9.3	570	296	
7/19	130	100	47	8.6	650	286	
7/21	140	100	45	10.0	622	342	Edema of shins and eyelids; headache; malaise
7/23	...	...	....	....	...	...	Delivered
7/27	135	100	33	9.3	555	380	
8/ 2	...	...	...	....	...	...	Blood nonprotein nitrogen, 38.4 mg. per 100 c.c.; urine, slightest possible trace albumin; report from Mass. Gen. Hosp.: "no evidence of chronic nephritis"
Mrs. D.	Very severe toxemia.			Convulsions.			
7/11	170	150	51	10.8	670	329	Slight tinge of bile in plasma, slight trace urinary albumin
7/13	220	170	....	....	...	...	Bled, 420 c.c.
	160	140	46	9.4	612	330	Had a convulsion after the delivery of dead fetus
7/15	120	100	39	9.0	560	336	Still dangerously ill
7/17	125	90	43	12.8	760	435	Rise here probably due to birth trauma and infection; temperature 101
7/21	110	85	45	8.5	508	280	Clinically much improved; renal function, 40 per cent.

the highest fibrin values are recorded for this case. The severity of the symptoms and the degree of fibrin elevation run parallel in this small series of observations.

Table 5 gives fibrin values obtained on succeeding days in four cases of true toxemia of pregnancy of varying grades of severity. Table 6 gives interval readings in two cases of nephritis during pregnancy.

The difference in the figures obtained in nephritis and those found in patients with true toxemia of pregnancy indicates that the underlying pathologic physiology in these two conditions is in all probability dissimilar.

The most severe case of eclampsia studied gave a high rather than a low blood fibrin value, contrary to what might be expected in severe liver injury. This fact would indicate that the symptoms in these patients are probably not due to liver insufficiency. This opinion is supported by the observation that the two patients with acute liver atrophy, while showing typical symptoms of liver insufficiency, did not have convulsions. It is noteworthy in this connection that none of the animals in Foster and Whipple's experiments with livers injured by

TABLE 6.—*Fibrin Values in Two Cases of Pregnancy with Nephritis*

Date	Blood Pressure: Systolic	Blood Pressure: Diastolic	Hematocrit Red Blood Cells, per Cent.	Fibrin: Average Two Determinations, Mg.	Fibrin: 100 C.c. Plasma, Mg.	Fibrin: 100 C.c. Blood, Mg.	Remarks
Mrs. C. R.	Clinically very ill.						
7/ 3	160	100	34.6	6.8	396	256	Urine, slight trace albumin and rare cast
7/ 5	170	110	40.5	7.8	460	248	Phthalein test, 40 per cent. 1-25; blood urea "normal"
7/ 5	...	...	....	....	...	...	Delivered by cesarean
7/13	130	100	34.0	10.1	635	430	Wound septic
1/25	120	90	....	....	...	...	Urine, slight trace albumin and casts
Mrs. Can.	Clinically very ill.						
7/ 2	175	110	41.5	6.8	405	242	Urine, slightest possible trace albumin; edema
7/ 3	175	110	41.5	5.6	334	199	
7/ 5	190	110	47.0	8.6	515	278	
7/ 7	175	110	44.4	7.4	445	249	
7/ 8	...	...	....	....	...	...	Delivered
7/ 9	140	100	43.0	8.0	480	274	
7/11	150	94	44.5	7.75	475	264	Blood nonprotein nitrogen, 39.3 mg. per 100 C.c.
7/13	170	120	42.0	7.7	455	262	
7/15	160	110	43.0	6.2	368	210	
7/17	170	110	42.0	6.6	394	228	
2/20	184	96	....	....	...	...	Urine, slightest possible trace albumin

chloroform anesthesia or phosphorus died when the fibrin content of the blood remained above normal. It was only when the liver injury was severe enough to cause a low blood fibrin that death occurred.

The postpartum fibrin rise, recorded in Tables 5 and 6, is probably best explained as being due to the trauma incident to birth, for injury to any tissue excepting the liver causes an increase in the fibrin. If infection is present, this postpartum rise is still more marked (see Mrs. D., Table 5).

The patients with nephritis were equally as sick, judging from clinical evidence, as the case of "severe toxemia" (Mrs Mc., Table 5). But it will be noted that the fibrin value in the latter was 622 mg. per hundred cubic centimeters of plasma or 342 mg. per hundred

cubic centimeters of whole blood, while the highest value in the former was 515 mg. per hundred cubic centimeters of plasma or 278 mg. per hundred cubic centimeters of whole blood. An estimation of the blood fibrin should, therefore, aid in the differential diagnosis of toxemia of pregnancy and nephritis accompanying pregnancy. Inspection of Gram's [4] determinations reveals evidence to support such a possibility. He reports two cases of nephritis complicating pregnancy, with plasma fibrin values of 580 and 480 mg. per hundred cubic centimeters or a whole blood fibrin figure of 290 mg. per hundred cubic centimeters in both cases. His one case of toxemia of pregnancy had a plasma fibrin of 700 or a whole blood fibrin of 390 mg. per hundred cubic centimeters.

FIBRIN VALUES IN LIVER ATROPHY

Two cases of liver atrophy, with subsequent necropsy, showed subnormal fibrin levels in both plasma and whole blood. In one patient very vigorous treatment with arsphenamin was the probable cause of atrophy, while in the other patient the etiology was not known. Table 7 gives the results in Case 1.

TABLE 7.—*Fibrin Values in a Case of Acute Liver Atrophy*

Date	Temperature, F.	White Blood Count, per Cu. Mm.	Fibrin	
			Per 100 C.c. Plasma	Per 100 C.c. Blood
November 27	98.6	.....	208	90
November 28	99.0	.....	250	125
November 29	99.4	8,800	135	67
December 1	100.0	7,300	280	140
December 4	102.5	13,700	356	188

CASE 1.—R., a man, admitted to Massachusetts General Hospital, had had arsphenamin treatment. Because infection influences the fibrin curve, the temperature and white blood cell counts are included in the table. It will be noted that with the onset of a terminal infection, as indicated by the rising temperature and white count, the fibrin level rose. A similar reaction was observed by Foster and Whipple [1] in dogs with experimental liver injury, when sterile abscesses were produced by the subcutaneous injection of turpentine.

Necropsy.—Liver: The organ weighed 900 gm. (normal from 1,300 to 1,400 gm.). The surface in places was granular and the edges thin and sharp. On section there was some increase in consistency. The sectioned surfaces did not show definite evidence of softening. Vessels were engorged. Gallbladder and ducts were normal. Microscopic sections of the liver showed central degeneration over wide areas; in a few sections, restricted areas of cirrhosis and many bile ducts. Lungs: The pleura showed a thick fibrinopurulent exudate adhering to the surface. On section, the lung was moist but no pneumonia areas were seen or felt.

CASE 2.—Mrs. D., an Italian housewife, aged 48, was admitted to Massachusetts General Hospital, with a history of liver atrophy. By our method of analysis only a few shreds of fibrin were recovered. So small was the amount of fibrin present that quantitative estimation was impossible although determinations were attempted on three consecutive days.

Necropsy.—The liver weighed 700 gm. The capsule generally was rather smooth except toward the margins where there was some fine wrinkling. Showing through the capsule here and there were small, discrete, brownish-red areas. Elsewhere the surface showed a dull, reddish color. On section, these brownish-yellow areas were found to be slightly softer than the surrounding, more nearly normal appearing tissue. The gallbladder and ducts were negative. The bile was thick and stringy.

Microscopic examination showed the absence of hepatic cells over wide areas. The tissue in such areas consisted almost entirely of a hemorrhagic stroma in which were groups of structures like bile ducts. In places islands of liver cells were present. One or more of the sections showed liver tissue in which were areas devoid of liver cells and infiltrated with mononuclear cells. Examination of kidney, spleen and pancreas was negative.

FIBRIN VALUES IN POSTARSPHENAMIN JAUNDICE

Five cases of postarsphenamin jaundice were studied. None of these cases were deeply jaundiced and none were fatal. During 1920 and 1921 twenty cases of jaundice from arsphenamin were observed in this hospital. The typical symptoms in these cases were malaise and anorexia, followed in two or three days by jaundice. Some patients noticed had light colored stools and dark colored urine; a few had infrequent attacks of vomiting. The time that elapsed after the last arsphenamin injection and the development of jaundice varied from one to ninety-one days. Jaundice in the nonfatal cases persisted from twenty to sixty days. The course of the disease, after entrance to the hospital, in the fatal cases was from four to twelve days. From five to twelve intravenous treatments of 0.4 gm. of arsphenamin or 0.6 gm. of neoarsphenamin had been administered.

The fibrin values in the nonfatal cases studied were all above normal, indicating that the liver damage was not very severe. Table 8 gives the fibrin values for five of the cases studied. The findings in other cases were similar.

In considering these data it will be recalled that the gallbladder and bile ducts were normal in Mr. R. Further, Gram [4] reports (Table 52) four cases of catarrhal jaundice with an average plasma fibrin of 380 mg. per hundred cubic centimeters and an average blood fibrin of 210 mg. per hundred cubic centimeters. One case of catarrhal jaundice studied by the author had a plasma fibrin of 387 mg. per hundred cubic centimeters, or a blood fibrin of 176 mg. per hundred cubic centimeters. Five duplicate determinations were made on this case during one week, from which this average was computed. These results seem to indicate that postarsphenamin jaundice is due to parenchymal liver injury and not to pathologic changes in the bile ducts.

FIBRIN VALUES IN LOBAR PNEUMONIA

It has long been known that pneumonia is associated with high blood fibrin. Foster and Whipple [1] (Paper 4, Table 53) give the results

TABLE 8.—*Fibrin Values in Five Post Arsphenamin Jaundice Cases*

Date	Age	Stage of Syphilis	Arsphenamin Received, Gm.	Mercury Received, Grains	Phthalein Renal Function, per Cent.	Stool Color	Temperature, F.	Urinary Albumin	Hematocrit Red Blood Cells, per Cent.	Fibrin: Average Two Determinations, Mg.	Fibrin: Per 100 C.c. Plasma, Mg.	Fibrin: Per 100 C.c. Blood, Mg.	Remarks
Case 1													
2/11/21	60	Late tertiary	1.8	6	60	Gray	99	Very slight trace	42.5	10.35	624	358	Liver not palpable
2/12/21	..	.....	...	..	..	.....	98	.....	44.0	9.8	585	326	
2/14/21	..	.....	..	..	..	.....	97.8	.....	44.5	7.3	438	243	
2/15/21	..	.....	...	..	..	.....	97.4	.....	45.5	5.0	340	185	
Case 2													
1/29/21	53	Late tertiary	1.2	6	45	Light brown	99	None	50.0	6.75	415	207	Liver dulness at sixth rib; edge felt 2 cm. below costal margin
1/30/21	..	.....	...	..	..	.....	100	.....	49.0	7.3	486	248	
2/ 1/21	..	.....	...	..	..	.....	98.8	.....	51.0	6.5	410	200	Coagulation time 9 minutes
2/ 2/21	..	.....	...	..	..	.....	98.6	.....	48.0	7.0	428	222	Stool guaiac test negative
2/ 3/21	..	.....	...	..	..	.....	99	.....	51.0	7.15	444	217	
Case 3													
7/ 9/20	32	Late secondary	1.8	15	..	Brown	98.6	None	53.0	5.9	370	174	Most severe case; very toxic; liver dulness at fifth rib; edge not felt
7/11/20	..	.....	...	..	..	.....	99	.....	50.0	7.7	490	245	Clinically better
7/13/20	..	.....	...	..	..	.....	99	.....	50.0	8.2	510	255	Almost free from jaundice
Case 4													
6/10/20	25	Late secondary	1.2	5	35	Light brown	98.6	Slight trace	46.0	6.4	400	213	Liver dulness from fifth rib to costal border
6/12/20	..	.....	...	..	..	.....	98	.....	47.0	6.8	415	220	
6/16/20	..	.....	...	..	..	.....	99	.....	47.5	7.2	445	234	
6/21/20	..	.....	...	..	..	.....	98.8	.....	45.0	7.2	444	244	
Case 5													
6/16/20	52	Tabes dorsalis	...	..	..	Light yellow	99	Very slight trace	45.5	6.45	400	218	Liver edge felt 7 cm. below costal border
6/21/20	..	.....	...	..	..	Light brown	98.6	.....	49.5	6.9	420	208	
6/23/20	..	.....	...	..	..	.....	98	.....	49.0	7.6	460	236	
6/26/20	..	.....	...	..	..	.....	97	.....	50.5	7.5	464	230	

obtained in nine cases of influenzal pneumonia. All these cases showed high fibrin levels. The average of their series was 1,046 mg. of fibrin per hundred cubic centimeters of plasma or 498 mg. of fibrin per hundred cubic centimeters of blood. All of these cases were fatal. Gram [4] (Table 34) reports twenty-two determinations on patients with influenzal pneumonia with the average reading of 620 mg. of fibrin per hundred cubic centimeters of plasma or 370 mg. of fibrin per hundred cubic centimeters of whole blood. He also reports, in Table 16 of his paper, seven determinations on cases with lobar pneumonia with an average plasma fibrin of 1,050 mg. per hundred cubic

TABLE 9.—*Fibrin Values in Four Cases of Lobar Pneumonia*

Duration of Disease, Days	Temperature, F.	White Blood Cells	Hematocrit Red Blood Cells, per Cent.	Fibrin: Average Two Determinations, Mg.	Fibrin: 100 C.c. Plasma, Mg.	Fibrin: 100 C.c. Blood, Mg.	Remarks
E. M. Lobar pneumonia Type I, complicated by empyema							
5	103	2,400	47	13.0	780	411	100 c.c. Type I serum intravenously
6	103	3,300	47	....	...	...	180 c.c. Type I serum intravenously
7	101	3,700	43	10.6	640	364	180 c.c. Type I serum intravenously
8	99.4	2,400	44	8.7	535	297	
9	100.4	2,500	44	7.0	425	238	
11	99.6	2,300	44	8.9	535	296	Cough; chest pain
13	100.6	2,000	41	8.5	500	294	Fluid signs in chest
14	99.6	.....	43	9.1	544	310	
15	.....	.....	..	....	...	...	600 c.c. fluid withdrawn
Case W. M.							
3	104 rectal	17,000	48	17.8	1,083	565	
4	105 rectal	20,000	45	10.4	645	354	Clinically much improved
Case E. M.							
9	100.5	2,300	51	16.6	1,060	519	Atypical Type II pneumococcus; tubercle bacilli found in sputum
11	102.4	3,300	50	7.3	450	225	Temperature on three previous days below 100
17	100	2,800	57	9.6	620	264	Temperature 101 next day
21	99.6	1,400	37	6.5	385	244	Patient comfortable, but very weak
Case W. M.							
Post crisis	98.6	.....	50	7.05	438	219	Blood chlorid normal 2/6/21
			47	5.6	339	179	2/9/21

centimeters or an average whole blood fibrin of 610 mg. per hundred cubic centimeters. All workers have found a high blood fibrin during the active stage of lobar pneumonia.

In the present study, the blood fibrin rapidly dropped to a normal or nearly normal level following an uncomplicated crisis. Any complication, such as empyema accompanied by fever, caused the fibrin level to rise again. It will be noted that the fibrin curve and the white blood cell curve did not run parallel in all instances.

Table 9 gives the results obtained in one case of Type 1 pneumococcus pneumonia and three cases of Type 2 pneumococcus pneumonia.

FIBRIN VALUES IN A MISCELLANEOUS GROUP OF DISEASES

Table 10 gives the results of fibrin determinations on a miscellaneous group of patients. Only four cases of this group had fibrin values below normal. These were patients with splenic anemia, cirrhosis of the liver, interstitial hepatitis (syphilitic), and severe secondary hemorrhage.

SUMMARY

1. The average *blood* fibrin for normal men was found to be 163 mg. per hundred cubic centimeters; for normal women, 179 mg. per hundred cubic centimeters. Variations of 25 mg. above or below these

TABLE 10.—*Fibrin Values in a Miscellaneous Group of Diseases*

Disease	Fibrin			
	Per 100 C.c. Plasma, Mg.	Per 100 C.c. Blood, Mg.	Red Blood Cells, per Cent.	Remarks
Cirrhosis	435	272	35	
Cirrhosis	435	236	48	Ascites
Alcoholic cirrhosis	380	226	40	Temperature 100
Cirrhosis	236	113	52	
Interstitial hepatitis	233	146	37	Syphilitic
Malignancy of pancreas	570	302	47	Jaundiced
Chronic obstructive jaundice	305	206	41	
Metastic carcinoma of liver	356	222	38	
Carcinoma of stomach (?)	800	545	38	Greatly enlarged liver
Splenic anemia	212	131	39	
Splenic anemia	480	385	19	
Secondary anemia	243	155	36	
Hemophilia	530	370	30	
Polycythemia	423	76	?	
Postdiarsenal jaundice	624	358	42	
Postdiarsenal jaundice	415	207	50	
Postdiarsenal jaundice	535	172	68	Died of pneumonia
Syphilis	443	212	52	Visceral
Syphilis	472	200	57	Visceral
Syphilis	395	202	49	Nerve
Syphilis	459	227	50	Nerve
Syphilis	432	220	49	Nerve
Pneumonia	1,063	565	48	Type II; third day of disease
Pneumonia	1,050	519	51	
Pneumonia	438	219	50	Posterisis
Pneumonia	789	417	47	
Encephalitis	333	153	54	
Encephalitis	440	211	52	
Pyelitis	715	372	48	Probable bronchopneumonia
Septic wound	635	420	34	
Typhoid	615	284	54	

figures may be said to be within normal limits. The average *plasma* fibrin found for normal men was 332 mg. per hundred cubic centimeters; for normal women, 344 mg. per hundred cubic centimeters. Variations of 50 mg. above or below these figures are probably within normal limits.

2. The average blood fibrin of *pregnant women* was found to be 273 mg. per hundred cubic centimeters; the average plasma fibrin, 415 mg. per hundred cubic centimeters. These figures will probably be found to hold true for the last months of pregnancy only.

3. *Toxemia of pregnancy* (nonfatal) is associated with an elevated blood fibrin. The elevation seems to parallel the severity of the symp-

toms. The toxic manifestations due to nephritis complicating pregnancy are not accompanied by a marked fibrin elevation. It is inferred from the difference in fibrin reaction that the toxic syndrome due to nephritis complicating pregnancy is of a different nature than that of true toxemia of pregnancy.

4. Two fatal cases of *acute liver atrophy* were associated with a low blood and plasma fibrin content.

5. Nonfatal *arsphenamin jaundice* was associated with an elevated blood and plasma fibrin. It is inferred from necropsy material and by comparison with cases of catarrhal jaundice that it is the liver parenchyma and not the bile ducts that are diseased in this condition.

6. Lobar pneumonia was associated with a greatly elevated blood fibrin. The fibrin rapidly falls to normal after uncomplicated crisis. Complications (e. g., empyema) cause a subsequent fibrin rise. The fibrin curve does not parallel the white blood cell count in all instances.

7. A series of fibrin determinations on a miscellaneous group of diseases is tabulated.

STUDIES IN FUSIFORM BACILLI AND SPIROCHETES

IX. THEIR RÔLE IN PULMONARY ABSCESS, GANGRENE AND BRONCHIECTASIS *

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In a study of infections with the fusiform bacillus and spirochetes, an exceedingly important group were the lesions in the lungs in which these micro-organisms were found. The following report is the result of a combined clinical and pathologic study of thirty-seven cases of fusospirochete pulmonary infections. It is hoped that this study will clarify certain hitherto obscure pulmonary infections, particularly those characterized by abscess formation and gangrene, and establish these infections as a definite clinical entity, comparable to the pneumonic processes caused by the pneumococcus, streptococcus and tubercle bacillus. In previous studies [1] the association of fusiform bacilli and spirochetes in putrid and gangrenous lesions of the body was emphasized, particularly in connection with such processes about the teeth, tonsils, middle ear, lungs and genitalia. At that time it was pointed out that these organisms were important etiologic agents in certain types of pulmonary lesions, characterized by necrosis and foul expectoration. We have conducted further investigations in these interesting but imperfectly understood pulmonary conditions. It was stated that these processes were often the result of lowered resistance in locations where these organisms normally reside or can readily enter. In connection with the respiratory lesions, the infections appear to arise largely from the organisms that reside in the mouth and upper respiratory passages.

About the teeth, these organisms were among the first to be recognized as normal inhabitants. They are especially numerous in heavy tartar deposits and about carious teeth and diseased gums. The tartar, when examined fresh, presents brushlike processes having central strands with coccoid and fusiform bodies arranged about the terminals.[1] Smears reveal large numbers of coarse and fine spirochetes, fusiform bacilli of various types, leptothrix filaments, and gram-positive streptococci. Anerobically, the fusiform bacilli produce a putrid odor in tissue media. The streptococci are usually of the viridans type, only occasionally of the hemolytic variety.

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1. Davis, D. J., and Pilot, Isadore: Studies of Bacillus Fusiformis and Vincent's Spirochetes, J. A. M. A. **79**:944-951 (Sept. 16) 1922.

In the faucial tonsils, we first noted these organisms in large numbers in the granular masses lying in the crypts, which in their appearance are like actinomyces granules. These bodies are found in 30 per cent. of extirpated tonsils and at some time are probably present in all individuals. They appear as foul, gray or yellow, single or multiple granules, from 1 to 6 mm. in diameter, lying in the depths or near the mouths of the crypts from which they may be expressed. Microscopically, they are made up of filaments arranged in ray-like structure not unlike actinomyces but containing no true branching threads. Filamentous organisms form a central shaft, about which small comma-shaped, fusiform and large diplococcoid bodies are arranged perpendicularly. Throughout are enormous numbers of fusiform bacilli and spirochetes together with diplococci. The spirochetes are gram-negative and actively motile. The cocci are chiefly streptococci of viridans or hemolytic type, the former often anerobic in early cultures. The bacilli are demonstrable in smear or culture in 80 per cent. of extirpated tonsils.[2] It would seem that a process similar to that of tartar formation occurs in the tonsil with the formation of spherical structures in the crypts instead of a film. In the nasopharynx, the fusiform bacilli are found in 32.6 per cent. and spirochetes in 5 per cent.[2]

PATHOGENICITY OF THESE ORGANISMS

It is not surprising, therefore, that with these organisms normally about tonsils and teeth that under certain conditions these bacteria find their way to the lower respiratory tract and give rise to definite lesions. In the extensive literature on pulmonary abscess and gangrene, only a few authors have noted the bacteria associated with or underlying these conditions. For the most part, the general impression was held that the ordinary pyogenic organisms such as staphylococci, streptococci, *B. influenzae* and pneumococci were largely responsible, occurring in mixed flora. Little attention has been paid to the possible existence of certain anerobes as important etiologic agents.

Rona[3] reported two cases of pulmonary gangrene in which fusiform bacilli and spirochetes occurred.

Feldman[4] found spirochetes at the margin of the necrotic wall in pulmonary gangrene.

Buday[5] observed fusiform bacilli and spirochetes of various types in histologic studies of gangrene and abscess in thirty-five cases.

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2. Pilot, I., and Brams, J.: Studies of Fusiform Bacilli and Spirochetes IV. Occurrence in Tonsils and Adenoids, J. Infect. Dis. **33**:134-138 (Aug.) 1923.
3. Rona: Arch. f. Dermat. u. Syph. **74**:171-201, 1905.
4. Feldman: Wien. klin. Wchnschr., 1906.
5. Buday: Beitr. z. path. Anat. u. z. allg. Path. **48**:70-122, 1910.

Arnheim [6] found spirochetes identical with dental spirochetes in five cases of pulmonary gangrene.

In this country a few isolated observations were made by Fishberg and Kline [7] who reported two cases, and by Kline and Blankenhorn [8] who recently described four other cases. The observations made heretofore would make one believe that these lesions are rare, but our experience has shown that they are not uncommon.

The factors that determine such infection correspond to a large extent to those associated with pulmonary abscess and gangrene. Earlier works emphasized pneumonia as an etiologic agent. While we still meet these complications in pneumonia, the number of such cases is small compared to the total number observed. A far more important cause today is general anesthesia, particularly since operative procedures are performed much more frequently and tonsillectomy is greatly in vogue. In a few instances, infection in the form of abscess or gangrene is superimposed on certain pathologic lung states, such as bronchitis, bronchiectasis, tuberculosis and carcinoma; vascular changes in lungs such as infarction and diabetes may occasionally be the predisposing factor. Foreign bodies, perforating lesions into bronchi may carry the infection into the lungs. In not a few instances, the underlying predisposing factor is not demonstrable.

The association of these anerobes morphologically and culturally similar to those found about the teeth and tonsils in necrotic lesions of the mouth and in the lung would indicate that these organisms, while saprophytic under normal conditions, may become pathogenic agents. Because of this behavior, we prefer to refer to these organisms as opportunists. Their pathogenicity, however, is low, requiring in the experimental animal relatively large doses to produce lesions. The fusiform bacillus in pure culture has very little pathogenicity. Injected into the pleural cavity of the rabbit in large doses, little reaction aside from slight fibrinous exudation occurs. For the production of a putrid lesion, the addition of a pyogen, particularly the streptococcus, is necessary. The cocci when injected alone produce a serofibrinopurulent pleuritis with no odor. When spirochetes, fusiform bacilli and cocci are combined the lesion is putrid. The pathogenicity of such mixtures was determined by injecting macerated granules of the tonsils and tartar deposits which showed such organisms in smear and culture, intrapleurally into rabbits. A putrid empyema resulted in a few days,

6. Arnheim: Zentralbl. f. Bakteriol. u. Parasitenk. **19**:20-34, 1911.

7. Fishberg, Maurice, and Kline, B. S.: Spirochetal Pulmonary Gangrene, Arch. Int. Med. **27**:61 (Jan.) 1921.

8. Kline, B. S., and Blankenhorn, M. A.: Spirochetal Pulmonary Gangrene, J. A. M. A. **81**:719-723 (Sept. 1) 1923.

Infection Observed in Patients Aged from Eight to Seventy Years

Case	Age	Sex	Color	Predisposing Factors	Pulmonary Lesion	Bacteriology	Termination	Therapy
1	18	♀	W	Tonsillectomy; nitrous oxid anesthesia	Abscess, right upper lobe	F. fusiformis, spirochetes, Streptococcus viridans	Recovery gradual	3 doses neo-arsphenamin
2	15	♂	C	Tonsillectomy; ether anesthesia	Abscess, right middle lobe	B. fusiformis, spirochetes, cocci	Recovery gradual, spontaneous	
3	24	♂	W	Tonsillectomy; ether anesthesia	Abscess	B. fusiformis, spirochetes, streptococci	Sudden rupture; recovery	
4	10	♂	W	Tonsillectomy; ether anesthesia	Abscess, left lower lobe	B. fusiformis, spirochetes, Streptococcus viridans	Sudden rupture; recovery	
5	44	♀	W	Tonsillectomy; ether anesthesia; subacute arthritis and endocarditis	Multiple abscess, both lungs	B. fusiformis, Streptococcus hemolyticus	Death	
6	28	♀	C	Hysterectomy; ether anesthesia	Abscess, right lower lobe	B. fusiformis, spirochetes, streptococci	Recovery spontaneous	
7	32	♂	W	Appendectomy; ether anesthesia	Gangrene of right lung	B. fusiformis, spirochetes, Streptococcus viridans, B. capsulatus (few)	Death	4 doses neo-arsphenamin, temporary improvement only
8	40	♀	C	Hysterectomy; ether anesthesia	Diffuse gangrene, right upper lobe	B. fusiformis, spirochetes, streptococci	Death	
9	48	♂	W	Herniotomy; ether anesthesia	Pulmonary abscess, right upper lobe	B. fusiformis, spirochetes, cocci	Improved	6 doses neo-arsphenamin
10	53	♂	W	Perforation of esophageal carcinoma	Gangrenous bronchopneumonia, right upper lobe	B. fusiformis, cocci, Gram negative bacilli	Death	
11	46	♂	W	Foreign body	Abscess, right lower lobe	B. fusiformis, spirochetes, Streptococcus viridans	Sudden rupture; recovery	
12	16	♂	W	Foreign body; tonsillectomy	Abscess, right lower lobe	B. fusiformis, spirochetes, Streptococcus hemolyticus and viridans	?	
13	68	♂	W	Bronchiectasis	Gangrenous bronchopneumonia, both lungs	B. fusiformis, spirochetes, S. hemolyticus (few), S. viridans (many), Staphylococcus albus (few), Gram-negative bacilli (few)	Death	
14	29	♀	W	Bronchiectasis; pregnancy	Multiple abscess, right middle and lower lobes; cerebral abscess	B. fusiformis, spirochetes, S. hemolyticus, pneumococci (few), S. albus (few), diphtheroids (few)	Death	
15	39	♂	W	Bronchiectasis; ether anesthesia	Diffuse gangrene of right lung; cerebral abscess	B. fusiformis, spirochetes, B. influenzae (few), S. viridans, S. hemolyticus (few)	Death	
16	55	♂	C	Bronchiectasis; perforation of abscess into bronchus	Gangrene of right lung	B. fusiformis, spirochetes, S. viridans, B. influenzae	Death	
17	25	♀	W	Bronchiectasis	Bronchopneumonia; Multiple abscesses (?)	B. fusiformis, spirochetes, S. hemolyticus and S. viridans, Micrococcus catarrhalis (few)	Improved	6 doses neo-arsphenamin
18	44	♂	W	Bronchiectasis	Multiple cavities, right lower lobe; bronchopneumonia	B. fusiformis, spirochetes, S. viridans	Improved; recurrence	6 doses neo-arsphenamin

19	50	♂	C	Diabetes	Gangrenous bronchopneumonia, right lung	B. fusiformis, spirochetes, S. hemolyticus, pneumococcus (few)	Death	
20	57	♂	W	Pulmonary infarct; cardiac decompensation	Infarction of right lung with gangrene	B. fusiformis, streptococci	Death	
21	..	♂	..	Bronchogenic carcinoma of lung; bronchiectasis	Gangrenous bronchopneumonia, right lung	B. fusiformis, streptococci, B. influenzae	Death	
22	..	♂	..	Bronchogenic carcinoma of lung	Multiple putrid abscesses	B. fusiformis, spirochetes, S. viridans	Death	
23	25	♀	C	Chronic ulcerative pulmonary tuberculosis	Pulmonary gangrene	B. tuberculosis, B. fusiformis, spirochetes, S. viridans, M. catarrhalis (few)	Death	3 doses neo-arsphenamin
24	38	♂	W	Chronic fibrocaseous pulmonary tuberculosis	Diffuse gangrene of right lung	B. fusiformis, B. tuberculosis, spirochetes, S. hemolyticus, S. albus (few)	Death	
25	13	♂	C	Tonsillectomy; miliary tuberculosis of lungs; bronchiectasis	Multiple putrid abscesses; putrid empyema	B. fusiformis, spirochetes, S. viridans, S. albus (few), diphtheroids (few)	?	
26	45	♂	W	Chronic ulcerative pulmonary tuberculosis; bronchiectasis	Multiple putrid abscesses	B. tuberculosis, B. fusiformis, spirochetes, S. viridans, S. albus	?	
27	34	♂	W	Chronic ulcerative pulmonary tuberculosis	multiple abscesses	B. tuberculosis, B. fusiformis, spirochetes, streptococci	Improved	Sodium cacodylate
28	38	♀	W	Lobar pneumonia	Multiple abscesses	B. fusiformis, spirochetes, S. viridans, B. capsulatis	Death	
29	30	♂	W	Lobar pneumonia (?)	Putrid abscess of right lower lobe; lobar pneumonia, right upper and middle lobes	B. fusiformis, spirochetes, S. hemolyticus, pneumococcus (few)	Recovery	Neo-arsphenamin
30	52	♂	W	Acute bronchitis (?)	Putrid abscess of right lower lobe	B. fusiformis, spirochetes, S. hemolyticus (few), S. viridans	Improved	7 doses neo-arsphenamin, pneumothorax
31	50	♂	W	Trauma to chest	Multiple putrid abscesses of left lower lung	B. fusiformis, S. viridans, staphylococcus (few), M. catarrhalis (few)	Death	
32	32	♂	C	Bullet wound of chest	Gangrene, right lung; right putrid pyopneumothorax	B. fusiformis, spirochetes, S. viridans	Death	Surgical
33	37	♀	W	Fall with fracture of forearm	Multiple putrid abscesses	B. fusiformis, spirochetes, S. viridans	Death	Surgical
34	32	♂	C	None determined	Multiple gangrenous abscesses of right lung	B. fusiformis, spirochetes, S. viridans and S. hemolyticus	Death	
35	34	♂	C	Urethral stricture ascending pyelonephritis	Gangrenous bronchopneumonia, both lungs	B. fusiformis, spirochetes, S. hemolyticus, B. capsulatus	Improved	2 doses neo-arsphenamin
36	53	♂	W	None determined	Pulmonary abscess, right lower lobe	B. fusiformis, spirochetes, S. viridans, S. hemolyticus	Improved	4 doses neo-arsphenamin
37	29	♂	W	"Cold" (?)	Pulmonary abscess, right lower lobe	B. fusiformis, spirochetes, cocci		

* In this column, ♀ indicates female; ♂ male

and in the pus spirochetes, bacilli and cocci were demonstrable.[1] The spirochetes seemed to disappear first, followed by the fusiform bacilli, leaving only the coccal forms. The cocci showed an aggressive tendency, advancing to the opposite pleura, into the pericardium and into the general circulation while the others were confined to the injected side. The tartar from carious teeth, an emulsion made of membrane from Vincent's angina and the sputum from pulmonary gangrene, produced the same type of reaction. Subcutaneously necrotic, sloughing lesions were produced in the guinea-pig by the same material. From these observations, it would seem that we are concerned with a combination of organisms which thrive in symbiosis producing in the tissues a constant putrid lesion. We must recognize, therefore, that lesions may arise not only from pure cultures of bacteria but also from two or more organisms in symbiosis.

Predisposition to fusospirochete infection depends on a multitude of factors, many of which are combined in individual cases. As a rule, the patients are not robust, but often undernourished and weakened by other causes. Acute respiratory infections may lower the general resistance. Diabetic patients are especially susceptible. The infection was observed in patients from 8 to 70 years of age in both sexes. The colored race appears to be quite susceptible (see table).

Local factors are of the utmost importance. Carious teeth and pyorrhea, conditions in which the anerobes may be found in great abundance, were outstanding findings in many patients but are by no means necessarily associated. Heavy tartar deposits may occur, while in some the teeth appear to be in good condition. The tonsils apparently do not play as important a rôle as the teeth. In a few, the crypts were distended with the foul granules rich in anerobes. Such tonsils may be responsible particularly for the pulmonary lesion following tonsillectomy.

The normal lung does not harbor these organisms. In fourteen pairs of lungs, free from any infectious process, no fusiform bacilli or spirochetes were demonstrable. In certain abnormal states these bacteria may establish a habitat in the bronchi. In bronchiectasis, they may lead a saprophytic existence and be demonstrated in the sputum, although no necrotic process or abscess formation is associated. The sputum as a rule in such instances is not foul. In old standing chronic bronchitis and in the sputum of bronchial asthma they may also be found, although no odor is produced. If patients with these bronchial conditions develop an acute infection of the respiratory tract either from some virulent autogenous or exogenous micro-organism or virus, or if the general resistance becomes decidedly lowered, the saprophytic anerobes often first cause a putrid bronchitis, spread through the

necrotic mucosa into the lung parenchyma, with the production of single or multiple foci of suppuration or gangrene.

The diseased parenchyma of the lung is decidedly inclined to become infected secondarily. Malignancy, tuberculosis and pneumonia may be complicated by abscess or gangrene. It is remarkable, however, that the anerobes only rarely cause superimposed infection in the tuberculous, although the streptococcus, staphylococcus and *B. influenzae* are commonly associated with the tubercle bacillus. Pneumonia of the lobar type is very seldom complicated by fusospirochete infection. Primary carcinoma of the lung, on the other hand, especially the bronchogenic type is often terminated by such secondary infection.

POST-TONSILLECTOMY ABSCESS

Inspiration of secretions of the mouth during general anesthesia is a frequent occurrence, particularly in tonsillectomy. In some, even with care, a small amount may be a nucleus for a pulmonary abscess. In others the large quantity or dose aspirated is the chief factor, particularly in children who are in good health.

In our experience the bacteria underlying post-tonsillectomy abscess or gangrene have usually been fusiform bacilli and spirochetes associated with streptococci. The condition manifests itself in a few days following the operation with cough, elevation of temperature (from 101 to 103), increase in pulse rate, general lassitude and polymorphonuclear leukocytosis. Distinct pain in the chest is often felt. Physical findings depend on location of the lesion, and often at this stage are absent or indefinite. From the tenth to the fifteenth day expectoration may come gradually or suddenly with the production of liquid sputum of foul or peculiar sweet odor. Smears made at this period reveal many streptococci, various forms of fusiform bacilli and spirochetes. The spiral forms may vary in number, often occurring sparsely among the more constant bacilli. The streptococci are usually of the viridans type. The expectoration continues for several days or weeks. In those with sudden rupture the condition may clear quickly. In four of the patients this abscess appeared single with recovery of all. In one, the abscesses were multiple, causing death on the eighteenth day. In one, arsphenamin was employed with good results.

The following cases are presented briefly.

REPORT OF CASES

Case 1.—A girl, aged 18 years, developed a cough, foul expectoration, and pain in the right chest fourteen days after tonsillectomy under gas anesthesia. Sputum formed three layers and contained numerous fusiform bacilli, spirochetes and streptococci. Her condition during the next two weeks became worse. Roentgen-ray examination revealed a large abscess with a cavity in the right upper lobe (Fig. 1). She was given three doses of neoarsphenamin

(0.6 gm.). Improvement was immediate after the first dose, with a fall in the temperature and less expectoration. In a roentgenogram, taken four weeks after the first injection, the abscess had disappeared (Fig. 2). The patient has remained well for the last eighteen months.

CASE 2.—A youth, aged 15, colored, complained of cough, pain in the left chest, fever and foul expectoration about three weeks after tonsillectomy under ether anesthesia. There was expectoration of large quantities of foul, gray-green sputum in which many bacilli, spirochetes and cocci appeared. Physical

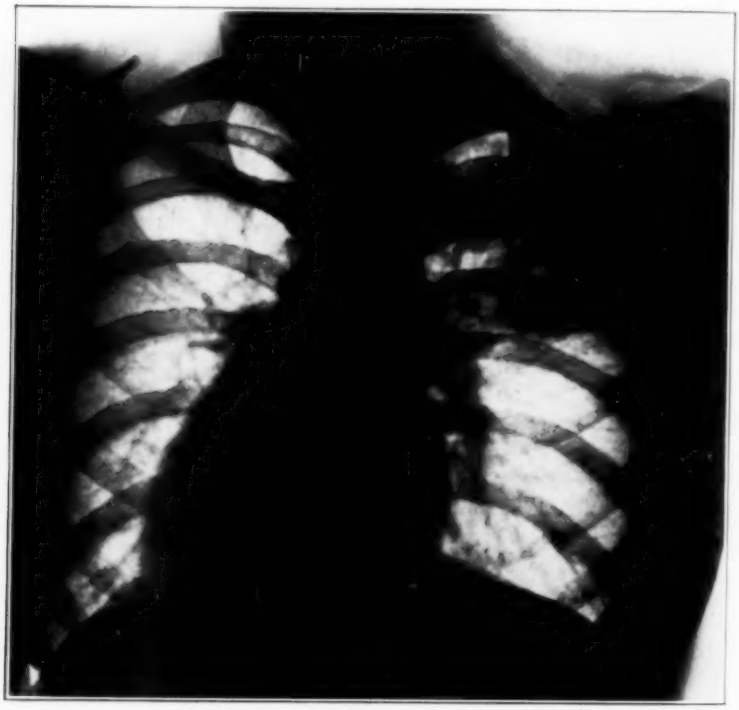

Fig. 1 (Case 1).—Post-tonsillectomy pulmonary abscess in right upper lobe before neo-arsphenamin therapy.

and roentgen-ray examination disclosed an abscess with cavity in the right middle lobe. Expectoration gradually became less, the temperature dropped to normal in the next two days, with fewer physical signs although the roentgenogram still revealed considerable pathologic changes. The patient left the hospital and did not report for subsequent examination.

CASE 3.—A man, aged 24, who had tonsillectomy performed under ether anesthesia, developed considerable weakness. While at work two weeks later, he suddenly expectorated a large quantity of foul sputum. A sample revealed numerous spirochetes, fusiform bacilli, and streptococci. Expectoration ceased the next day; recovery was rapid with no further symptoms.

CASE 4.—A boy, aged 10, developed a temperature of 102.4 F. ten days after tonsillectomy under ether anesthesia. Fever, cough and some pain continued for four days, when suddenly he expectorated 4 ounces (118.4 c.c.) of foul pus, containing fusiform bacilli, spirochetes and cocci. Physical and roentgen-ray examination presented signs of consolidation and a small amount of fluid in the left lower chest. The temperature dropped and expectoration ceased in twenty-four hours. Examination five weeks later gave no physical or roentgen-ray findings.

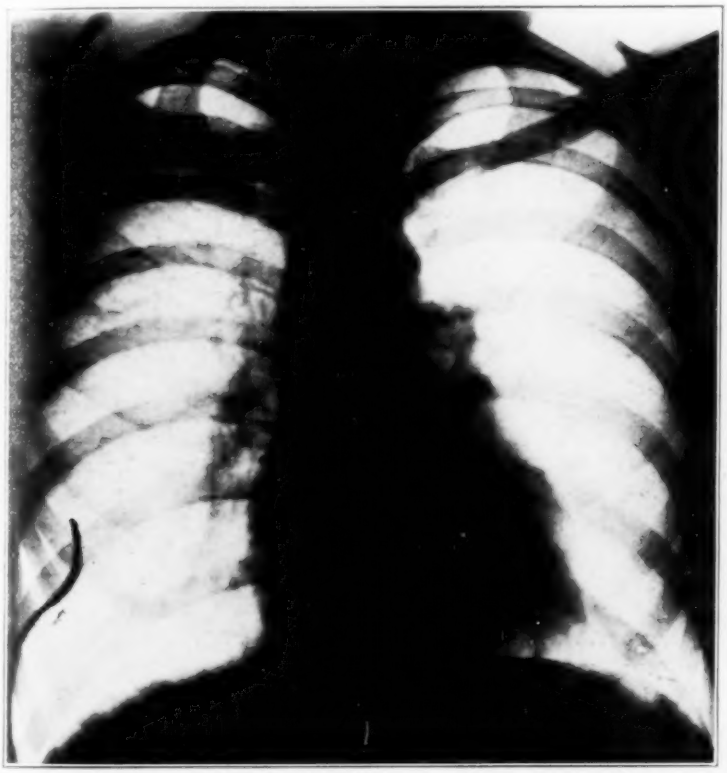

Fig. 2 (Case 1).—Post-tonsillectomy abscess after neo-arsphenamin therapy.

Comment.—In Case 4 the abscess discovered on physical and roentgen-ray examination was obscured by the presence of fluid in the pleural cavity. The large amount of pus suddenly evacuated would indicate an abscess of fair size.

CASE 5.—A woman, aged 44, was ill for several weeks with subacute polyarthritis and mitral endocarditis. After a normal temperature lasting for two weeks, tonsillectomy was performed. Arthritis recurred immediately. Nine days later she began to bleed from the tonsillar fossa for forty-eight hours. Six days later the temperature rose to 104 and the respirations became labored. Death ensued in three days. Anatomic diagnosis at necropsy was multiple

abscesses of the left lung and right upper lobe (Fig. 3). Smears and cultures of pus of necrotic centers of abscesses revealed fusiform bacilli and hemolytic streptococci but no spirochetes.

Comment.—The lesions in the lung were among the earliest observed. Beginning necrosis was evident. The numbers of bacteria, while considerable, did not compare with the masses seen in older lesions.

The mode of infection in post-tonsillectomy pulmonary abscess is largely aspiration of throat secretions. The frequency of abscess complicating throat surgery is due to the massive doses of bacteria

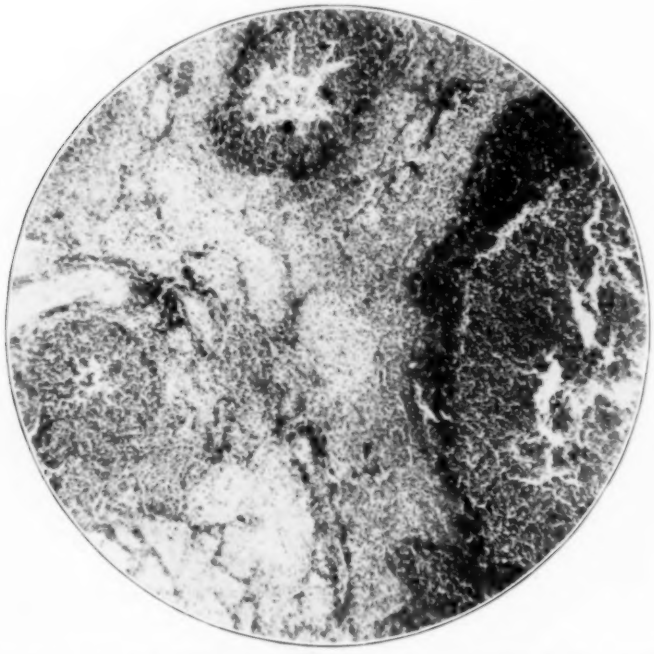

Fig. 3.—Multiple abscesses following tonsillectomy. These were among the earliest lesions observed. The centers show begining necrosis, and in smears revealed fusiform bacilli and cocci in large numbers (hemotoxylin and eosin).

that can be aspirated. That aspiration is responsible is further substantiated by the development of abscess and gangrene resulting from ether anesthesia, in which the operative procedure was not in the throat or respiratory tract. It is possible that pulmonary infarction may have played a contributory rôle, but in none of the patients clinical symptoms or physical or roentgen-ray findings could be found indicating such complication.

In the three cases, pulmonary abscess or gangrene complicated abdominal operation, and in one a herniotomy, all under ether anesthesia. A brief review of these cases is presented.

Case 6.—P. R., a woman, aged *28*, colored, had hysterectomy performed under anesthesia for fibroids. Within two weeks she developed clinical and roentgen-ray evidences of pulmonary abscess in the right lower lobe. The sputum was foul and contained fusiform bacilli, spirochetes and streptococci. She made a spontaneous recovery within a month after the onset.

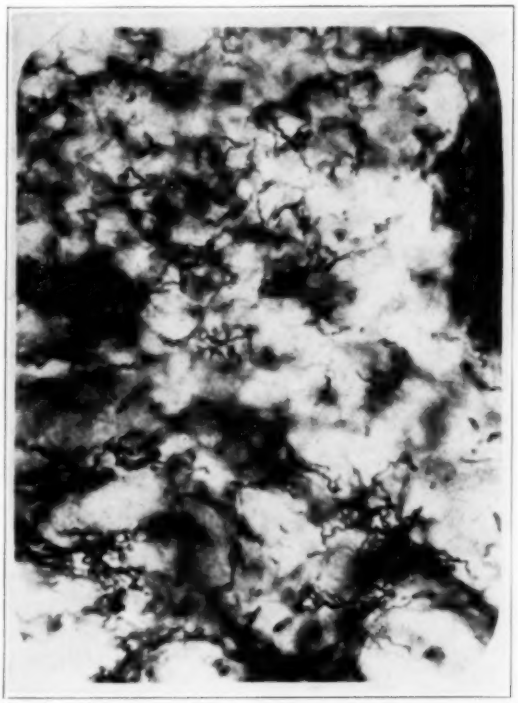

Fig. 4 (Case 8).—Large masses of spirochetes observed in pulmonary gangrene.

Case 7.—J. P., a man, aged *32*, developed cough, foul expectoration and fever two weeks after appendectomy under ether anesthesia. Physical and roentgen-ray examination revealed extensive consolidation of the right lung, with the formation of multiple cavities. The sputum was profuse, intensely foul and green. Fusiform bacilli, spirochetes, together with streptococci and gram-negative bacilli were abundant. Neoarsphenamin treatment was started four weeks after onset. Four doses were administered, but only temporary improvement was obtained. Death resulted from toxemia.

Case 8.—L. W., a woman, aged 40, colored, developed pain in the chest, cough, bloody expectoration eleven days after hysterectomy under ether anesthesia. Examination revealed extensive consolidation of the right upper lobe. Death occurred in three weeks. At necropsy the anatomic diagnosis was, gangrene of the upper lobe of the right lung, confluent bronchopneumonia of the lower lobe of the right lung. The gangrenous lesions presented in smears and Levaditi preparations enormous numbers of spirochetes (Fig. 4), fusiform bacilli, and streptococci. The bronchopneumonia was of the interstitial type (Fig. 5).

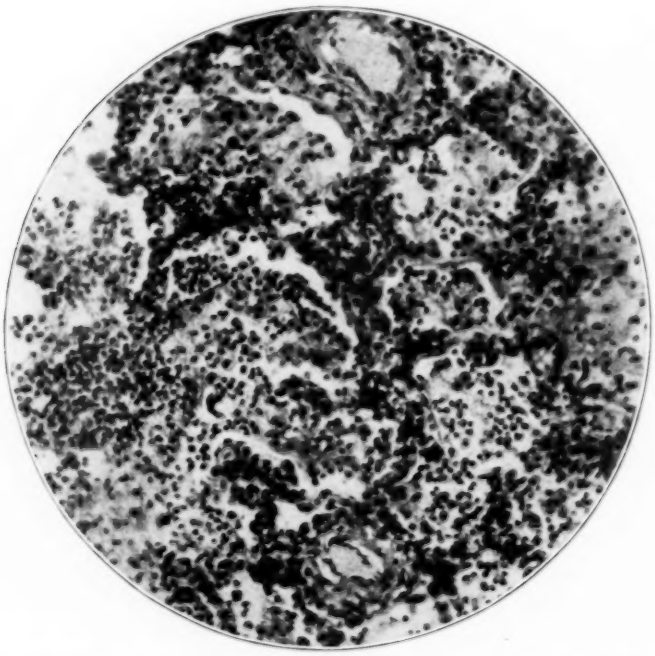

Fig. 5 (Case 8).—Interstitial bronchopneumonia associated with pulmonary gangrene. The cells infiltrating the septums were chiefly of the mononuclear type (H and E stain).

Case 9.—S. V., a man, aged 48, developed bloody, foul expectoration two weeks after herniotomy under ether anesthesia. Physical and roentgen-ray examination revealed a huge pulmonary abscess in the lower portion of the right upper lobe. The sputum contained cocci, fusiform bacilli and spirochetes. The patient was observed for four weeks, during which time he became worse and the lesion appeared more extensive. Six doses of neoarsphenamin were administered. A decided improvement resulted in four weeks. The temperature was normal, expectoration slight and physical and roentgen-ray signs of the abscess greatly diminished.

Perforating lesions into the trachea and bronchi lead to aspiration of material containing bacteria with the formation of pulmonary

abscesses or gangrenous bronchopneumonia. The bacteria concerned in such lesions are frequently the fusiform bacilli with or without spirochetes. Pulmonary lesions of this sort frequently terminate the clinical course of carcinoma of the esophagus. We have observed that fusiform bacilli and spirochetes of the mouth early infect the ulcerating lesions in the esophagus, causing necrosis with ultimate perforation into the trachea or bronchi and death from the pulmonary complication.

CASE 10.—C. F., a man, aged 53, complaining of inability to swallow for six months, developed pain in the chest, with cough and expectoration. Examination of the mouth revealed very carious teeth, marked pyorrhea and foul breath. A friction rub occurred over the right lower lobe posteriorly, together with a few moist râles. Blood examination revealed hemoglobin 60 per cent., red blood cells 3,310,000, leukocytes 13,500. Wassermann blood test was negative. The patient died about two weeks after the development of the pulmonary symptoms. At necropsy a primary carcinoma of the esophagus with a fistula leading into necrotic cavity of the right upper lobe was seen. The abscess cavity was foul smelling and gray-green. In smears many fusiform bacilli were found, together with cocci and short gram-negative bacilli. The middle and right lower lobe were involved in an acute bronchopneumonic consolidation. Levaditi sections revealed large numbers of typical fusiform bacilli and cocci in the gangrenous areas and short bacilli plus cocci in the nongangrenous foci. The esophageal mass was a typical squamous cell carcinoma with considerable necrosis.

Infections with these organisms associated with foreign bodies in the lung is illustrated in the following two instances.

CASE 11.—C. C., a man, aged 46, complained of pain in the right chest, cough, "fever and chills" occuring irregularly for five months. He had been entirely well until one day he felt that a "piece of meat" was sticking high up in the chest. He developed a cough, with slight expectoration and pain in chest about two weeks later. Examination revealed a well nourished man. The teeth were carious and associated with pyorrhea of moderate severity. In the chest there was flatness over the right lower lobe, with diminished fremitus and breath sounds. The temperature varied from 101 to 103; the pulse from 100 to 120. The leukocyte count was 23,400 per c.mm. With the roentgen ray, a dense shadow with fuzzy upper border was demonstrated in the right lower chest (Fig. 6). One ounce (30. c.c) of serofibrinous fluid was removed from this region which in smear revealed a few short chains of streptococci. Four days later, during a spasm of coughing, the patient suddenly expectorated a large amount of foul green pus together with an irregular piece of cancellous bone 6 mm. in diameter. The sputum revealed many fusiform bacilli, few spirochetes and streptococci. The temperature dropped to normal the following day, and physical signs of involvement rapidly disappeared in the following week.

Comment.—It is possible that the bone tissue from a chop was accidentally aspirated into the trachea, but more probably it was swallowed and arrested in the esophagus with subsequent ulceration into the lung.

CASE 12.—A. J., a youth, aged 16, complained of cough and putrid expectoration. The onset dated three years previously when he developed pain in the right lower chest, cough, and foul expectoration shortly after tonsillectomy. On

examination at that time there was dulness, moist râles and rhonchi over the right lower lobe. In the roentgen-ray film a foreign body was seen in the right bronchus. Bronchoscopy was performed and a small piece of wire 2 cm. long was extracted. No decided improvement followed until an artificial pneumothorax was performed. He returned, however, about a year later with recurrence of symptoms and physical signs. At this time sputum was obtained. It was intensely fetid and formed three layers. Tubercle bacilli were not found. Large numbers of fusiform bacilli, long chains of cocci and moderate numbers

Fig. 6 (Case 11).—Lung abscess in right lower lobe with serofibrinous pleuritis associated with foreign body.

of short slender and long coarse spirochetes were demonstrated. In cultures the colonies were predominantly *Streptococcus viridans* type with a few *Streptococcus hemolyticus*. The patient did not return for further observation.

Abscess and gangrene occasionally complicate other pathologic processes in the lung. In bronchiectasis, the anerobic bacteria are largely responsible.

CASE 13.—A man, aged 68, entered the hospital and died on the same day. A history of cough and expectoration for several years had been present. He became decidedly worse six weeks previously. The sputum was green and had a foul odor; no tubercle bacilli were found. At necropsy the anatomic diagnosis was: Diffuse bilateral bronchopneumonia with multiple foci of gangrene in both lungs; chronic diffuse bronchitis with moderate bronchiectasis; atrophic pulmonary emphysema; hyperplasia of the peribronchial lymph glands. In the right lung fibrin exudate occurred over the pleura of the lower lobe which was of doughy consistency with firm nodules. Section revealed two confluent cavities in the lower lobe filled with foul, dark, purulent material. Solid raised foci were seen throughout. The left lung presented similar cavities at the base with a small cavity in the apex but no caseous nodules.

Cultures of gangrenous areas gave many colonies of *Streptococcus viridans*, a few of *Streptococcus hemolyticus*, *Staphylococcus albus* and small gram-negative bacilli. In the anerobic slants straight and thread forms of *B. fusiformis* occurred.

Microscopic sections presented an interstitial bronchopneumonia with areas of necrosis in places made up of pus cells, débris and bacteria. Levaditi preparations showed many cocci, fusiform bacilli and spirochetes in the necrotic areas.

In the Cases 14 and 15 the bronchiectasis was associated with fusospirochete infection, with complication of metastatic brain abscess.

CASE 14.—A woman, aged 29, complained of inability to move the left arm, defective speech, headache and vomiting for three weeks. For two years she had had cough, with some loss of weight. Prior to the development of the cough, she had had an appendectomy, but any direct relation of respiratory symptoms to the operation could not be ascertained. Examination revealed a well-nourished woman in the sixth month of pregnancy. The chest presented impaired resonance, amphoric breathing and moist râles over the right lower lobe. Clubbing of fingers and toes was marked. The left arm was flaccid, and bilateral Babinski sign was present. The Wassermann blood and spinal fluid tests were negative. Globulin was found in the spinal fluid. The sputum was very foul; no tubercle bacilli were found. Blood analysis showed 65 per cent. hemoglobin, 3,250,000 erythrocytes, 6,800 leukocytes, with normal differential count. In the roentgen-ray plate multiple small bronchiectatic cavities were demonstratable in the right lower lobe. The temperature was 98.2 F., the pulse 78; respiration 22; blood pressure, systolic 94, diastolic 62.

The patient developed repeated convulsions and died nine days after admittance. At necropsy the anatomic diagnosis was: Multiple bronchiectatic cavities and abscesses of lower and middle lobe of right lung; abscess of right cerebral hemisphere; cloudy swelling of parenchymatous organs; 6 months old fetus in uterus.

The right pleural cavity was completely obliterated by firm, fibrous adhesions. The lung was consolidated in scattered areas in the middle and lower lobes. On cut section, numerous abscess cavities, from 2 to 4 cm. in diameter, filled with foul smelling pus were present in all lobes, but most numerous about the hilum, where considerable fibrosis was also observed (Fig. 7). The bronchi were thickened and the mucosa necrotic in places.

The brain weighed 1,400 gm. Over the right parietal lobe was an area of localized meningitis. One centimeter underneath was a soft area, which on section proved to be a putrid grayish green abscess, measuring 8 cm. in its anteroposterior and 5 cm. in the transverse and vertical diameters involving the cortex. The wall of the abscess was necrotic; and the blood vessels in these regions were dilated (Fig. 8).

Smears and cultures from several abscess cavities of the lung revealed typical and filamentous forms of *B. fusiformis*, various types of spirochetes,

Fig. 7 (Case 14).—Putrid abscesses complicating bronchiectasis.

Fig. 8 (Case 14).—Putrid cerebral abscess complicating putrid bronchiectasis.

Streptococcus hemolyticus and small numbers of pneumococci, *Staphylococcus albus*, and diphtheroids. In the brain abscess, cocci, and fusiform bacilli, but no spirochetes were found (Fig. 9).

Microscopic section of the brain revealed meninges thickened from exudate of pus cells, extending along the pia to the abscess. The wall of the abscess was made up of granulation tissue with an inner necrotic layer consisting of debris, bacteria and pus cells, and an outer layer of fibroblastic tissue infiltrated with lymphocytes and endothelial leukocytes. In Levaditi stains, cocci and fusiform bacilli but no spirochetes were found in the abscess wall.

Comment.—The pregnancy may have been an important predisposing factor. The chronic fusospirochete infection may become a severe generalized process, as in pulmonary tuberculosis.

Case 15.—N. C., a man, aged 30, complained of weakness in the right arm and leg for three weeks. Two months previously, under general anesthesia, he was

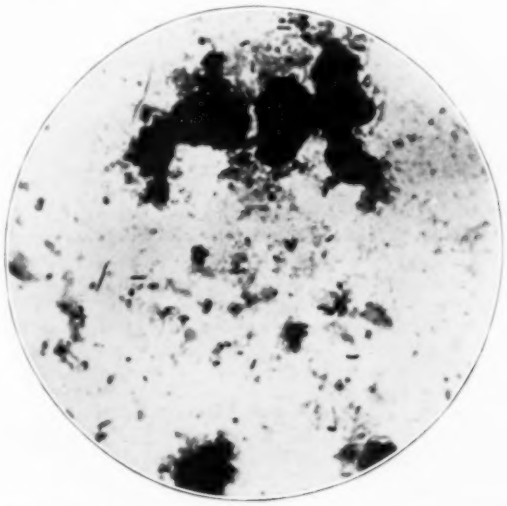

Fig. 9 (Case 14).—Smear from pus of cerebral abscess. Fusiform bacilli, cocci but no spirochetes are present.

operated on for subcutaneous abscess in the loin. While in the hospital it was noted that the patient coughed and expectorated large quantities of foul sputum. On physical examination, a right sided hemiparesis was noted. In the chest, impaired resonance and moist râles occurred over the right lung. A homonymous hemianopsia appeared, followed by the development of paralysis of the palate. The spinal fluid was under increased pressure, globulin was present, and cell count 200 per cubic millimeter. The Wassermann test was negative. The anatomic diagnosis at necropsy was as follows:

Extensive gangrene of the right lung; bronchiectasis of the right lung; cerebral abscess of the right parieto-occipital region; localized pachymeningitis; cloudy swelling of parenchymatous organs; right sided fibropurulent pleuritis; hyperplasia of tracheobronchial lymph glands; recent healed scar over the right lumbar quadrant of the abdomen; fibrous periappendicitis and perisplenitis.

The right pleural cavity contained yellow turbid fluid with fibrin, which on culture gave hemolytic streptococci. The right lung, on section, revealed the

necrotic upper lobe with a cavity 12 by 7 by 7 cm. The remainder of the lung was solid, of green color excepting the middle lobe which was involved in patches. The lining bronchi was covered by foul smelling brown purulent exudate. A few nongangrenous areas were gray, firm and elevated containing yellow pus. The left lung presented scattered areas of consolidation in the form of nodules, from 6 to 10 mm. in diameter. The left hemisphere of the brain contained an abscess 1.5 cm. in diameter filled with foul smelling pus. The surrounding brain substance was soft and yellow. Cultures of the spinal fluid revealed hemolytic streptococci.

In smears from gangrenous areas of the lung, enormous numbers of fusiform bacilli, spirochetes and cocci were seen; in bronchopneumonic areas the same bacteria in fewer numbers were found. Cultures revealed the predominance of *Streptococcus viridans*, a few hemolytic streptococci and small gram-negative bacilli (*B. influenzae*).

Microscopic section presented the walls of the bronchiectatic cavities lined by granulation tissue. The epithelium was ulcerated, and the underlying tissue infiltrated with round cells. Bronchopneumonic consolidated areas comprised alveoli, some of which were filled with serum, others with polymorphonuclear leukocytes, alveolar epithelium and fibrin. The interstitial tissue was infiltrated with lymphocytes. Other portions of the lung were made up completely of necrotic areas with large masses of blue staining tissue consisting of large masses of bacteria, pus cells, fibrin and necrotic tissue elements, lying free in the lumen. Many of the larger vessels were thrombosed, while the capillaries appeared engorged. Necrosis occurred in bronchial mucosa and large masses of bacteria filled the lumen.

In Levaditi preparation, the necrotic areas of the lung were composed of enormous numbers of bacteria. The bacilli were often comma shaped, others typical fusiform straight and curved. The spirochetes were most numerous at the margin of the necrotic mass and appeared to invade the neighboring regions through the interstitial tissue accompanied by few or no bacilli, and an occasional diplococcus. Some spirochetes were short and fine, others longer and coarser. The lumen of the bronchi contained similar organisms which occurred also in large numbers in the necrotic ulcers of mucosa. In the distant bronchopneumonic areas only cocci were seen.

The brain presented an abscess with the wall made up of an inner layer of lymphocytes and plasma cells and an outer layer of fibroblasts. The cellular infiltrate extended to the cortex. Moderate perivascular infiltration occurred. In Levaditi stains fusiform bacilli, cocci, but no spirochetes appeared in the abscess wall.

Comment.—General anesthesia undoubtedly lowered the resistance of the lung already bronchiectatic. That complication of fusospirochete gangrene often depends on multiple predisposition factors is well illustrated by this case.

In the next instance, the bronchiectasis was complicated by multiple abscesses with rupture into bifurcation of the trachea.

CASE 16.—E. M., aged 55, colored, complained of cough, foul expectoration, pain in the right lower chest with general symptoms of loss of weight and general weakness for three weeks. Physical examination showed dulness in the right upper lobe and a few râles throughout the right lung. The temperature varied from 99 to 101. The leukocyte count was 20,000 with differential count of 88 per cent. polymorphonuclear, 9 per cent. small mononuclear, and 3 per cent. large mononuclear leukocytes. Sputum, which was foul and green, was repeatedly examined for tubercle bacilli with negative results. In smear, fusiform bacilli, spirochetes and cocci were abundant. Cultures demonstrated small gram-negative bacilli (*B. influenzae*), *Streptococci viridans* and pleomorphic forms of fusiform bacilli.

Neo-arsphenamin (0.45 gm.) was administered but the patient was already desperately ill and succumbed two days later.

At necropsy the anatomic diagnosis was:

Multiple gangrenous abscesses in the right upper and lower lobe; gangrenous tracheitis; bronchiectasis of the right lung and right pyothorax; caseous tuberculosis of the peribronchial lymph gland; perforation of the trachea at bifurcation.

The ulceration through the trachea was accompanied by extensive peritracheal necrosis and gangrene of the adjoining pleura and lung. The mucosa at this point was green and necrotic. The right pleural cavity contained blood tinged foul smelling pus. The pericardial cavity contained 100 c.c. of fluid with a few fibrin flakes. The right lung presented numerous small abscess cavities at the apex and right lower lobe from 1 to 2 cm. in diameter. The middle lobe and left lung on section revealed a few raised areas of bronchopneumonia. In microscopic section the cavities were bronchiectatic, lined by granulation tissue consisting of round cells, young vessels and fibroblasts. Large areas of total necrosis were seen. In these regions the blood vessels were thrombosed. Alveoli were filled with exudate of fibrin, polymorphonuclear leukocytes and desquamated epithelium in the bronchopneumonic areas. Mucosa of the bronchi was necrotic and masses of bacteria occurred in the poorly stained areas.

Levaditi preparations showed many fusiform bacilli, a few spirochetes and many cocci in necrotic areas and margin of abscess wall.

In two patients with bronchiectasis the complicating fusospirochete infection was treated with neo-arsphenamin with favorable results.

Case 17.—V., a woman, aged 25, complained of cough and expectoration of large amount of foul sputum over a period of fourteen years. Prior to onset she had had empyema and a rib resection. Physical examination showed a patient, underweight, with many carious teeth, moderate pyorrhea and foul breath. In the chest impaired resonance and bubbling râles were found in the right lower lobe. Blood showed 84 per cent. hemoglobin, 4,560,000 erythrocytes per cubic millimeter, and 12,600 leukocytes with a differential count of 81 per cent. polymorphonuclear neutrophils; 3 per cent. basophils, 1 per cent. eosinophil; 12 per cent. small lymphocytes, and 1 per cent. large mononuclear. The Wassermann reaction was negative. Sputum varied from 6 to 8 ounces (from 178 to 240 cm.) daily, forming three layers. Smears revealed cocci, fusiform bacilli and spirochetes. In cultures *Streptococcus hemolyticus, Streptococcus viridans, Micrococcus catarrhalis* appeared. Roentgen-ray film showed increase in the hilum shadow with small bronchiectatic cavities in the right lower lobe near the hilum. Six doses of neo-arsphenamin (from 0.45 to 0.6 gm.) were administered intravenously. The odor of the sputum disappeared, the quantity diminished, and smears revealed fewer fusiform bacilli and complete absence of spirochetes. The râles in the chest were fewer; in the roentgen-ray film, however, little change was noted.

Case 18.—R. M., a man, aged 44, entered with a history of expectoration beginning seventeen years ago. Previously he had had pleurisy and pneumonia complicated by an abscess of the hip, and later by considerable cough and expectoration. He improved in a few months and was comparatively free from symptoms for six years. Profuse expectoration returned and continued for nine months. Up to four months prior to entrance to hospital he was in good general health except for an occasional paroxysm of cough and expectoration. For the last four months the expectoration was foul and often blood streaked. He improved after a brief stay, receiving three doses of neo-arsphenamin but returned about ten weeks later with very foul expectoration.

Examination then presented an undernourished adult white man with very foul breath. The teeth were covered with heavy tartar deposits. In the chest impaired resonance, increased vocal and tactile fremitus and cavernous breathing were found over the right lower lobe. Some moist, sibilant and sonorous

râles were scattered over the entire chest. The blood Wassermann was negative. Hemoglobin, erythrocyte and leukocyte counts were normal. The sputum formed three layers, was of a foul odor and revealed many cocci, fusiform bacilli and a moderate number of spirochetes. In cultures, the cocci appeared as pure *Streptococcus viridans*. A clinical diagnosis of bronchiectasis complicated by pulmonary abscess was made. Three doses of neo-arsphenamin (0.3, 0.5 and 0.6 gm.) were given. The odor and amount of expectoration were considerably reduced.

Comment (Cases 50 and 29).—It is, of course, obvious that neo-arsphenamin is no cure for bronchiectasis, but if the medication can control or diminish the putrid expectoration, it is certainly of great benefit to such patients.

Vascular changes and lowered resistance in a diabetic patient predispose to fusospirochete infection, with resulting pulmonary gangrene.

Case 19.—H. H., a man, aged 50, colored, complained of pain in the right chest, cough and profuse expectoration of foul green sputum for one month. For two years he had been aware of being a diabetic patient with typical symptoms of thirst, polyuria and weakness. Loss of weight became pronounced in the last three months. One year previously, he had noted numbness of the lower extremities especially of the feet. Urinary obstruction occasionally necessitated catheterization.

On examination, the patient appeared emaciated. The teeth were artificial, the breath foul. The chest presented dulness, diminished fremitus and breath sounds, with friction rub over the right lung. The urine contained large quantities of glucose, acetone, diacetic acid and a trace of albumin. The patient became comatose the following day. Glucose, sodium bicarbonate and insulin were administered but death occurred in twenty-four hours.

The anatomic diagnosis at necropsy was as follows:

Confluent bronchopneumonia of the right upper and lower lobe with multiple foci of gangrene; lobar pneumonia of the left middle lobe with gangrenous abscess; diffuse suppurative bronchitis; marked hypostatic edema and congestion of both lungs; acute serofibrinous pericarditis; atrophy of pancreas; copper-reducing substance in urine; emaciation; cloudy swelling of parenchymatous organs; acute hyperplasia of tracheobronchial lymph glands; healed tuberculosis of the apex of the left lung; moderate chronic diffuse nephritis; adenomatous hypertrophy in the median lobe of the prostate; hypertrophy of the musculature of the urinary bladder.

The right lung filled the pleural cavity. The pleura over the lower and middle lobe was covered with fibrinous exudate. The upper lobe was firm in the posterior and inferior portion. The middle was completely consolidated. The lower lobe contained irregular confluent nodules in the posterior portion. Section of the upper and lower lobes was grayish red with multiple areas green in color, from 1 to 3 cm. in diameter. The middle lobe contained a green abscess cavity 3.5 cm. in diameter, filled with foul detritus. The left lung presented a few scattered areas of consolidation in the lower lobe.

Smear made from the necrotic areas showed many types of fusiform bacilli, cocci, but few spirochetes. In cultures *Streptococcus hemolyticus*, few colonies of pneumococcus and *Staphylococcus albus* and pleomorphic forms of *B. fusiformis* were obtained.

Microscopic studies presented a picture of an interstitial bronchopneumonia, with areas of complete necrosis. The bronchopneumonic areas contained alveoli, some filled largely with serum, fibrin, a few polymorphonuclear leukocytes, many alveolar epithelial cells and endothelial leukocytes, others were densely packed with pus cells, fibrin, and débris. The alveolar walls were swollen, and the interstitial tissue infiltrated chiefly with lymphocytes and large mononuclear leukocytes. The cavitations were lined by necrotic tissue consisting of bacterial masses, fibrin, cellular débris and pus cells. Some portions are entirely

necrotic, staining poorly, surrounded by a dense cellular infiltrate. In many of the large vessels thrombosis had occurred and the capillaries appeared engorged.

Levaditi preparations revealed enormous numbers of bacilli and cocci in necrotic areas. The bacilli were typical fusiform, straight and curved, some long and thread-like, and many short comma forms. Few spirochetes occurred in the bacterial masses. At the margin, however, the bacilli became less numerous and the spirochetes predominated (Fig. 10). The latter increased in numbers from the margin to the bronchopneumonic areas for a short distance and then disappeared. Cocci were seen in remote areas of consolidation, often forming clumps in the alveoli.

Fig. 10 (Case 19).—Margin of abscess cavity in pulmonary gangrene revealing spirochetes migrating into less involved tissue while numerous fusiform bacilli and cocci occur in the necrotic areas (Levaditi stain).

A rare type of complication was the occurrence of gangrene in a pulmonary infarct in a patient with chronic cardiac decompensation.

Case 20.—J. W., a man, aged 57. The anatomic diagnosis was as follows: Intrapulmonary thrombosis of branches of pulmonary arteries, infarction of right lung with gangrene; chronic mitral and aortic endocarditis; passive congestion of the liver with brown induration; ascites; edema of the penis, scrotum and legs; slight icterus.

The right lung near the center of the anterior surface presented an area of 10 cm. in diameter, from dark green to black in color with a soft center. On section of this area a cavity was encountered, filled with foul, black material.

The walls were soft and greenish black. In one of the vessels leading to this region of the lung a thrombus was found. The remainder of the lung contained a few scattered, slightly nodular areas of bronchopneumonia.

Smears of the necrotic material revealed many streptococci, various forms of fusiform bacilli, but no spirochetes.

Of special interest was the occurrence of fusospirochete infection engrafted on carcinoma of the lung.

Case 21.—A. P., the anatomic diagnosis of whom was as follows: Primary bronchogenic carcinoma of the right upper lobe with metastasis in the mediastinal glands; bronchiectasis of the entire right lung, bronchopneumonia of upper and lower lobes with multiple foci of gangrene. Pressure on the vena cava, edema of the tissues of the head, neck, upper thorax and extremities, marked pyorrhea alveolaris.

Smears from necrotic areas revealed many cocci, short gram-negative bacilli (*B. influenzae*) and fusiform bacilli.

In microscopic sections there appeared confluent bronchopneumonic areas, with marked interstitial tissue infiltration. Areas of necrosis contained large masses of bacteria and débris. The alveoli were filled with fibrin, serum and polymorphonuclear leukocytes. The interstitial tissue was infiltrated with polymorphonuclear leukocytes. Large vessels contained thrombi, made up of fibrin, pus cells and bacteria (cocci and bacilli). Mucosa of the small bronchi was necrotic on the surface and densely infiltrated with cells in the deeper portions.

In the Levaditi sections many forms of fusiform bacilli, short, long and thread-like, together with cocci but no spirochetes could be demonstrated.

Case 22.—P., a man, complained of cough, foul expectoration, rapid loss of weight over a period of several weeks. The sputum was foul, formed three layers and contained many fusiform bacilli, cocci and a few spirochetes. In cultures *Streptococcus viridans* was obtained.

At necropsy, the right lung revealed bronchogenic carcinoma with multiple putrid abscesses. Similar organisms were observed in the abscess cavities, as in the sputum.

The association of fusospirochete infection with pulmonary tuberculosis, while rare, was encountered in five patients. The lesions complicating the tuberculosis were bronchiectasis, abscess and gangrene, and were described recently.[9]

The complications were observed in five patients. In the first, marked fetid expectoration was accompanied by far advanced pulmonary tuberculosis.

Case 23.—A woman, aged 25, colored, developed foul expectoration for the last few months in the course of tuberculosis of five years' standing. She was greatly emaciated and presented typical signs of cavities in left upper and right lower lobes. The sputum was intensely foul, of green color, and revealed numerous tubercle bacilli, in addition to large numbers of fusiform bacilli, spirochetes and cocci. Necropsy was refused. A clinical diagnosis of pulmonary gangrene superimposed in a far advanced ulcerative tuberculosis was made.

Case 24.—F. M., a man, white, aged 38, developed cough and foul expectoration two months prior to entrance to hospital. He was apparently in good health up to that time. The sputum was foul and green and contained tubercle bacilli, fusiform bacilli, cocci and very few spirochetes. The patient was given 0.9 gm. neo-arsphenamin but he was already desperately ill and died seven days after entrance. At necropsy there was a diffuse gangrene of the right lung and a chronic fibrocaseous tuberculosis of both upper lobes. Of special interest was the enormous numbers of spirochetes found in the lung, although

9. Pilot, I.; Davis, D. J., and Shapiro, I. F.: Am. Rev. Tuberc. **8**:249-259, 1923.

the sputum revealed only a few (Fig. 11). The fusiform bacilli and cocci, which were abundant in the sputum, occurred in the bacterial masses lining the gangrenous cavity, while spirochetes were numerous at the margin and away from the abscess wall. An emulsion of the gangrenous area injected experimentally into rabbits produced putrid lesions.

Fusospirochete infection was noted in three tuberculous patients with bronchiectasis.

Case 25.—A youth, aged 13, colored, developed cough, pain in chest and a fetid sputum following tonsillectomy. The sputum contained bacilli, spirochetes and cocci, but no tubercle bacilli were demonstrated. At necropsy the anatomic diagnosis was: Multiple putrid bronchiectatic cavities of both lungs; multiple putrid abscesses of the right lung; a right sided putrid empyema; miliary tuberculosis of all lobes, caseous tuberculosis of the peribronchial lymph glands.

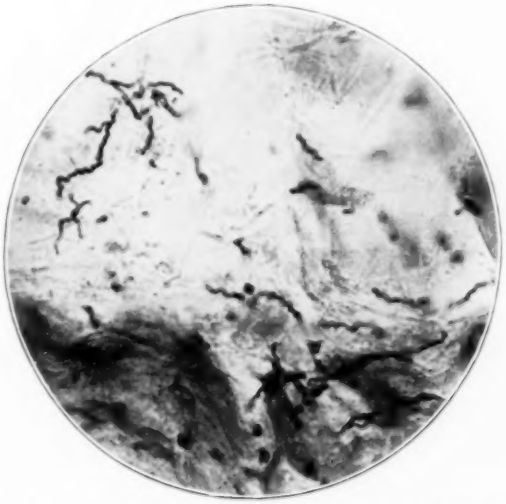

Fig. 11 (Case 24).—Spirochetes in tuberculous lung (Levaditi stain).

Case 26.—A man, aged 45, white, had a cough and profuse expectoration for three years. A fetid odor was noticed at intervals. While under observation he had a temperature of from 103 to 104 with foul breath, fetid expectoration, and on physical and roentgen-ray examination many small bronchiectatic cavities in the right lung. The sputum formed three layers, and contained many fusiform bacilli, spirochetes, cocci and a moderate number of tubercle bacilli.

Case 27.—A man, aged 34, gave a history of cough and foul expectoration for two years. Physical and roentgen-ray examination presented dense infiltration of both upper lobes with a small cavity formation. The sputum formed three layers and contained fusiform bacilli, spirochetes, streptococci and tubercle bacilli.

Previous infection in the respiratory tract predisposes to fusospirochete infection. The incidence of such complication in bronchitis and

lobar pneumonia is surprisingly low. Indeed, it is often difficult to ascertain if the pulmonary abscess is definitely preceded or is associated with these conditions.

CASE 28.—M. P., a woman, aged 38, entered hospital Aug. 29, 1921, with clinical evidences of lobar consolidation of the left upper lobe. Resolution was delayed and it was thought that tuberculosis may have been the complicating factor. However, repeated sputum examinations for tubercle bacilli were negative. Physical findings became fewer, accompanied by the general improvement of the patient who was sent home. She remained without symptoms until one year later when she began to cough and expectorate profuse quantities of sputum which was often blood-tinged and foul. The temperature was 103.2, pulse 126, respiration 40. The breath was foul; the chest revealed dulness over the right lower lobe, impaired resonance over both upper lobes with amphoric breathing in the upper left lobe anteriorly. Moist râles were heard over the right lower lobe in the axillary region, and over the left upper lobe anteriorly. The sputum was extremely foul, of large quantity, green, and in smears contained cocci, fusiform bacilli and a few spirochetes. The cultures aerobically showed *Streptococcus viridans*, *B. capsulatis* and anerobically *B. fusiformis*. The blood picture was that of secondary anemia, with 60 per cent. hemoglobin, 3,160,000 erythrocytes, and 10,400 leukocytes. A diagnosis of multiple abscesses was made. She was given sodium cacodylate, two and a half grains daily, subcutaneously. Improvement was gradual with a fall in temperature to 100; less expectoration and fewer râles in the chest. After six weeks the sputum was still of considerable quantity but not foul. Leukocyte count at this time was 7,400. In the following four weeks the temperature became normal and the sputum less profuse. Physical and roentgen-ray findings of cavitations near the hilum of the left lung were still present when the patient was discharged.

CASE 29.—I. K., a man, aged 30, entered with a history of cough, foul smelling sputum and pain in the right chest for three months. Apparently shortly before the onset of foul expectoration he had suddenly developed a chill with pain in the chest and cough, a clinical picture like that of lobar pneumonia.

Examination disclosed a well nourished man, with very foul breath. Carious teeth and marked pyorrhea were striking. In the chest, dulness occurred over the right lower lobe with crepitant and large moist râles in the right lower and middle lobes. Sputum contained fusiform bacilli, and cocci but no spirochetes or tubercle bacilli. The temperature varied from 101 to 104; the pulse from 100 to 120; respiration from 36 to 40. The blood examination gave 75 per cent. hemoglobin, 3,400,000 erythrocytes and 13,400 leukocytes. The Wassermann test was negative. In the roentgen-ray film a dense shadow involved the lower half of the right upper lobe, merging gradually into more normal tissue. The right pleural cavity had a fluid level. The patient rapidly became worse as the pleural cavity filled.

The anatomic diagnosis at necropsy was as follows:

Putrid abscess of the right lower lobe with rupture and right pyothorax; resolving pneumonia of the right lower lobe; lobar pneumonia of the right middle and upper lobes, right fibrous and fibrinous pleuritis; hypostatic bronchopneumonia of the left lower lobe; fibrinous pleuritis of the left pleura; acute hyperplasia of the tracheobronchial lymph glands; latent tuberculosis of peribronchial lymph glands, cloudy swelling of parenchymatous organs; pyorrhea alveolaris.

On removal of the right lung, a large abscess cavity containing thick, foul, creamy pus was opened. The cavity was situated in the posterior lateral surface of the right lower and middle lobes, measuring 24 cm. long by 17 cm. wide and deep and communicating with the pleural cavity which contained similar

pus. The visceral pleura was covered with fibrinous exudate. The cut surface of the upper and middle lobes were consolidated except for apex and anterior margin.

Smears of the pus revealed cocci, fusiform bacilli and a few spirochetes. In aerobic cultures *Streptococcus hemolyticus* predominated and a few pneumococci appeared; anerobically, pleomorphic forms of fusiform bacilli occurred.

In microscopic section of the abscess region the picture was that of interstitial bronchopneumonia extending from the necrotic abscess wall. The alveoli were filled with polymorphonuclear leukocytes, fibrin, bacteria and epithelium. The interstitial tissue was infiltrated with round cells, largely lymphocytes. The bronchi were lined by granulation tissue and contained masses of bacteria free in the lumen. The blood vessels showed moderate endarteritis. In Levaditi preparations the pyogenic wall was made up of enormous masses of bacteria, consisting of a mixture of bacilli, cocci and spirochetes. The spirochetes showed no migrating tendency. Cocci, however, were found in the more remote consolidated areas.

Comment.—The course appears to have been first pneumonia, later a local gangrene in the involved lobe with terminal lobar and lobular consolidation in the other lobes.

Case 30.—J. D., a man, aged 52, a butcher, entered with a history of cough, pain in right chest and fever for ten days. The cough was at first nonproductive. Later, slightly purulent sputum was expectorated.

During the first week of observation, the temperature remained at 102 or 103 F.; the pulse from 86 to 100. Blood examination gave 21,300 leukocytes, 85 per cent. hemoglobin. Expectoration increased and was noted to be distinctly foul. The sputum was blood tinged and formed three layers. Smears revealed 90 per cent. polymorphonuclear leukocytes, cocci, fusiform bacilli, spirochetes and diphtheroids. In cultures the cocci appeared predominantly *Streptococcus viridans* with a few colonies of *Streptococcus hemolyticus*. Roentgen-ray plates showed clouding of the central portion of the right lower lobe, extending from the fourth costochondral junction to the fifth interspace anterior and from the hilum shadow to the periphery of the chest. The upper margin of shadow was rather definitely outlined. The lower margin was lost in a diffuse haziness, then gradually faded out toward the dome of diaphragm. In the center of the shadow there was a circumscribed area of decreased density, about 2 cm. in diameter, and just medial to that two more similar areas 1 cm. in diameter. No fluid level was demonstrable. The left lung was clear.

The patient was immediately placed on neo-arsphenamin therapy. Improvement was rapid. Roentgen-ray plates in seven days showed a diminution in the extent of findings. Density was smaller and cavitations less distinct. The temperature and pulse at this time were normal. The cough and expectoration ceased. Four weeks later the shadow had almost completely disappeared, and aside from thickening of the pleura no abnormal physical findings could be elicited.

In three patients trauma may have played a rôle as a predisposing factor. The injuries may, however, have been coincident. The history, as given by the patient, would seem to indicate that fusospirochete infection may follow an injury, particularly to the chest.

Case 31.—C. M., a man, aged 50, white, complained of cough, pain in the chest and weakness for two months. He attributed his symptoms to the result of an injury by an iron door that fell on his back. A cough started one week later. Thre weeks later foul expectoration appeared. Physical examination disclosed a fairly well-nourished man, with very foul breath. Several teeth were carious, tartar deposits heavy, and there was pyorrhea of moderate severity. The chest revealed dulness over the left lower lobe posteriorly, with crepitant râles in this region and in the right axilla. There was slight edema of the ankles. Blood pressure was 110 systolic and 80 diastolic. The tempera-

ture varied from 98 to 101, with elevation in the afternoon; the pulse from 80 to 100. The urine was normal. The blood count showed 56 per cent. hemoglobin, 3,968,000 erythrocytes, 14,700 leukocytes; differential count of 70 per cent. polymorphonuclears, 22 small lymphocytes and 8 large mononuclear leukocytes. The sputum averaged 12 ounces (355 cm.) daily, forming three layers of grayish green color, was of foul odor and contained many elastic fibers. Smears of teeth and surface of tonsils showed many bacilli, spirochetes and diplococci. Repeated examinations of the sputum were negative for tubercle bacilli and spirochetes. Large numbers of fusiform bacilli, however, were

Fig. 12 (Case 31).—Multiple abscesses of lung.

present. In cultures, *Streptococcus viridans* was predominant, associated with a few colonies of hemolytic staphylococci and micrococcus catarrhalis. Roentgen-ray film demonstrated irregular cavities in the lower portion of the left lung (Fig. 12). The right lung was emphysematous. A diagnosis of multiple abscesses was made.

Neo-arsphenamin (0.9 gm.) was administered once a week for seven weeks. Improvement was distinct. Expectoration was less foul and the temperature was lower (from 98 to 99). An artificial pneumothorax was then performed and repeated in one month. The sputum diminished in amount, was only slightly foul and in smears revealed fewer fusiform bacilli. Two months later

expectoration was only slight and had no odor. Roentgen-ray film showed a partially collapsed lung. The patient left the hospital and did not return for further observation.

Case 32.—A man, aged 32, colored, complained of sharp pain in the left chest, cough and shortness of breath for a period of one month. Previous to onset of the cough he had noticed loss of strength and had a tired feeling. He had a sudden paroxysm of coughing one evening, which lasted for fifteen minutes. Expectoration did not begin until two weeks later. In the past history, it was noted that he had been shot in the chest. He did not recall the pulmonary symptoms following the shooting. Three years later he had a definite hemoptysis. Physical examination revealed dulness and a few inconstant râles over the right apex. Flatness and decreased breath sounds were elicited over the right lower lobe.

The temperature varied from 100 to 103, the pulse from 90 to 130, respirations from 24 to 38, leukocyte count was 11,300. The sputum was green, liquid, very foul and contained many fusiform bacilli, spirochetes and cocci. Smears from the teeth showed an abundance of the same organisms.

Roentgen-ray film demonstrated the fluid level of a pyopneumothorax up to the second costal cartilage on right side with displacement of the heart to the left. The pus aspirated from the pleural cavity was very foul, green, and in smears showed large numbers of bacilli, spirochetes and cocci. Aerobic cultures gave no growth. Anerobic blood agar cultures gave *Streptococcus viridans* and fusiform bacilli. Cultures of sputum showed similar organisms.

The patient died three days after admittance. Necropsy was refused.

Case 33.—M. S., a woman, aged 37, white, complained of cough, foul odor to breath, and expectoration of large quantities of foul sputum. Two years previously she had fallen on ice breaking her right forearm, but apparently had had no direct injury to the chest. Four months later she became ill with pain in the chest, followed by cough and foul expectoration within four weeks. Lung abscess was the diagnosis at that time and some relief followed a direct aspiration. On physical examination the patient appeared fairly well-nourished. Several teeth were carious, some pyorrhea was noted. The chest presented dulness and moist râles over the right lower lobe. In the roentgenogram the apices were clear and the right hilum shadow increased. In the right lower lobe a shadow was evident, 8 by 10 cm. in size, extending to the level of the third rib anterior and fifth rib posteriorly containing small abscess cavities. The temperature varied from 99 to 100, the pulse from 80 to 110. The blood count presented 75 per cent. hemoglobin, 4,070,000 erythrocytes, 9,450 leukocytes; differential count of 88 per cent. polymorphonuclears, 7 per cent. large lymphocytes, 4 per cent. transitionals and 1 per cent. eosinophils. The sputum was of green color and liquid, containing a small piece of gangrenous lung tissue. Smears from this portion revealed large numbers of spirochetes, fusiform bacilli and cocci in large masses. The aerobic cultures contained *Streptococcus viridans* and the anaerobic, streptococci and typical fusiform bacilli.

Surgical drainage was attempted, but death ensued twenty-four hours later. No necropsy could be obtained.

The development of fusospirochete infection in the lung without any well-defined predisposing factors is of special interest. In some patients perhaps, bronchitis existed without any definite knowledge of this on the part of the patient, or an upper respiratory infection not severe enough to impress the patient. On the other hand, the anerobes and associated pyogens may have attained an added virulence under certain conditions sufficient to invade the apparently normal lung. It is

also possible that these organisms may cause lesions in persons whose general resistance has been greatly lowered. The two fatal cases were in colored persons who appeared to have low resistance. The first patient in whom we observed gangrene due to these organisms did not give any history or evidence of predisposing factors.

Fig. 13 (Case 34).—Early stage of pulmonary gangrene.

CASE 34.—G. C., a man, aged 32, colored, complained of cough and blood-tinged expectoration, pain in the chest and loss of weight, which had developed gradually five months previously. No history of bronchitis, pneumonia or anesthesia could be obtained. Physical examination presented a fairly well nourished man. Several teeth were carious and some pyorrhea alveolaris was present. The breath was extremely foul. The chest revealed impaired resonance of the right upper lobe, bronchovesicular breathing and crackling râles over this region. The sputum was blood streaked, of foul odor and contained numerous fusiform bacilli and spirochetes, and gave gram-positive cocci but no tubercle bacilli. The blood count was 7,200 leukocytes and 4,520,000 erythrocytes. In an examination two weeks later, it was noted that the râles were

more numerous, extending over the entire right upper lobe and the upper part of the lower lobe. Roentgen-ray film showed a solid shadow extending to the hilum involving the same parts of the right lung (Fig. 13). One week later the films revealed a circular shadow in the right upper lobe about 5 cm. across, extending almost to the periphery. The temperature at this time was 100, pulse 84, respiration 24.

An attempt was then made to drain the abscess cavity through a rib resection. Two cubic centimeters of blood-tinged foul smelling pus was aspirated from the right upper lobe. Smears showed gram-positive diplococci, fusiform bacilli and spirochetes (Fig. 14). Aerobic cultures were sterile, while in the anaerobic cultures many colonies of *Streptococcus viridans* and fusiform bacilli were obtained.

Expectoration continued to be profuse and of foul odor (Fig. 15). The pus from the chest wound was of the same character. For a period of three weeks

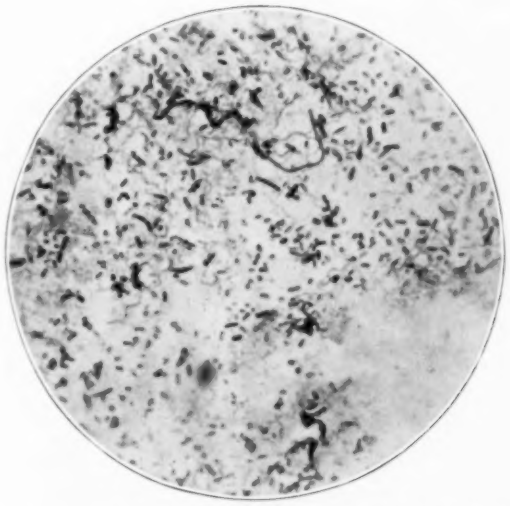

Fig. 14 (Case 34).—Smear of putrid pus aspirated from pulmonary abscess, revealing fusiform bacilli, spirochetes, and streptococci (carbolfuchsin stain).

the patient appeared to expectorate and drain less, and his general condition improved, with a normal temperature and pulse. He quickly developed signs of empyema, and from the right pleural cavity 1,600 c.c. of very foul pus was aspirated. The aerobic cultures of this pus were sterile. The patient died eight hours later.

The anatomic diagnosis at necropsy was:

Multiple gangrenous abscesses of the right lung, involving the upper and greater part of the lower lobe, putrid empyema (1,000 c.c. of pus) of the right pleural cavity, acute hyperplasia of the mediastinal lymph glands, emphysema of the left lung, left sided serofibrinous pleuritis (30 c.c. of turbid fluid).

Smears of pus from the abscess and from the right pleural cavity revealed gram-positive cocci, fusiform bacilli and spirochetes but no tubercle bacilli. In cultures *Streptococcus hemolyticus*, *Staphylococcus aureus* and fusiform bacilli aerobically were obtained.

Microscopic section presented confluent areas of interstitial pneumonia with foci of gangrene. In the abscess wall a mixture of fusiform bacilli, cocci and spirochetes appeared, while spirochetes were found in great numbers at the margin of the abscess.

In Case 35, the genito-urinary condition may have profoundly lowered the general resistance.

CASE 35.—S. D., a man, aged 34, colored, entered the hospital extremely ill, with a history of cough, pain in the chest for nine days, associated with headache, abdominal discomfort and vomiting.

Fig. 15 (Case 34).—Later stage of pulmonary gangrene after attempted surgical drainage.

Examination revealed a well-developed, delirious man. The lips were covered with herpes. The teeth had heavy brown deposits. The chest presented scattered areas of bronchovesicular breathing and moist râles over both lower lobes. A urethral discharge containing gram-negative diplococci was present. The temperature was 103.4, pulse 124, respiration 48; the blood showed 70 per cent. hemoglobin, 3,280,000 erythrocytes and 8,400 leukocytes; the culture was sterile. The patient died forty-eight hours after entrance, and at necropsy the anatomic diagnosis was as follows:

Multiple abscesses of both lungs, acute hyperplasia and edema of the tracheobronchial lymph glands; latent tuberculosis of the apex of the right lung; cloudy swelling of the liver and spleen; bilateral acute cysto-ureteropyelo-

nephritis; fibrous urethral stricture at the proximal end of anterior urethra with urinary extravasation; periurethral necrosis; hypertrophy and coarse trabeculations of urinary bladder.

The left lung contained numerous scattered button like nodules, which on section were dark red, raised areas with soft necrotic centers. The right lung contained similar nodules, from 2 to 6 mm. in diameter.

In smears made from the necrotic centers, fusiform bacilli, cocci, spirochetes and short gram-negative bacilli were demonstrated. Cultures contained *Streptococcus hemolyticus, B. capsulatis* and pleomorphic forms of *B. fusiformis.*

Sections showed confluent areas of bronchopneumonia with foci of necrosis. The alveoli contained serum, pus cells and desquamated epithelium. In the necrotic areas enormous numbers of cells and bacteria were found. The masses of bacteria formed structures similar to actinomyces granules but no true actinomyces were demonstrable. In Levaditi sections the actinomyces-like structures revealed a mixture of typical and thread forms of fusiform bacilli, short bacilli (*B. capsulatis*), cocci and spirochetes of various types. At the margin, chiefly spirochetes and a few short bacilli were found. In the adjoining consolidated areas the alveoli contained leukocytes and short bacilli resembling morphologically *B. capsulatis.*

In two other patients with lung abscess neo-arsphenamin was employed with favorable results.

Case 36.—J. R., a man, aged 53, white, complained of stench from mouth, cough, foul expectoration and pain in chest. The onset was gradual seven weeks previously with apparently no determining cause. He had had a nasal operation under local anesthesia three years prior to the present trouble. There were no complications.

Physical examination disclosed a well nourished, robust person. There were several carious teeth and marked pyorrhea. The tonsils were enlarged and slightly congested. The breath was very foul. The chest presented moderate emphysema and no dulness or râles were demonstrable. The fingers were clubbed. The temperature varied from 97 to 101; the pulse from 72 to 90. The urine contained a trace of albumin. The blood showed 60 per cent. hemoglobin, 3,570,000 erythrocytes, 17,600 leukocytes, with a differential count of 54 per cent. polymorphonuclear leukocytes, 20 per cent. small lymphocytes, 10 per cent. large mononuclears, 6 per cent. eosinophils, 4 per cent. basophils, and 6 per cent. transitional leukocytes. The Wassermann reaction was negative.

The sputum was foul and formed three layers. In smears many spirochetes, fusiform bacilli and cocci appeared. Aerobic culture contained equal numbers of *Streptococcus viridans* and *Streptococcus hemolyticus;* anerobic, pleomorphic forms of fusiform bacilli.

The roentgen-ray film presented a density in the deep portion of the right lower lobe, with a small cavity containing a distinct fluid level: Neo-arsphenamin (0.6 gm.) was administered. The sputum diminished in amount. The dose was repeated. The sputum remained foul and still contained bacilli and spirochetes. Roentgen-ray film, however, showed less cloudiness and no cavity or fluid level. Two weeks later, the expectoration was slight, temperature normal, and roentgenogram revealed still less cloudiness. The patient left the hospital and did not return for observation.

Case 37.—J. A., a man, aged 29, white, entered with a history of persistent cough, expectoration of foul, blood-tinged sputum, and sharp pains in the right chest. These symptoms came on gradually, following what the patient considered a mild cold six weeks previously. On examination, he appeared well nourished. The breath was foul and the teeth carious. The chest presented dulness, increased tactile fremitus, tubular breathing and coarse râles over the right lower lobe. The temperature was 99, pulse 90. Leukocyte count was 18,100 with 75 per cent. polymorphonuclear leukocytes. The sputum was foul. Smear showed numerous fusiform bacilli, cocci and a few spirochetes. Tubercle bacilli

were not found. In the roentgenogram the apexes were clear, the right cardiodiaphragmatic angle obscured by an irregular density in the right lower lobe. No cavity was demonstrable. Two doses of 0.45 gm. of neo-arsphenamin and two of 0.6 gm. were administered at intervals of from four to six days. Expectoration became less; the breath and sputum lost their foul odor; the cough diminished and the temperature became normal. Roentgen-ray examination revealed great reduction in the density, while the physical signs greatly diminished.

BACTERIOLOGY

The bacteriologic studies were made of the sputum and the tissues at necropsy by smears and cultures. Aerobic cultures were obtained on 10 per cent. blood agar plates by streaking the washed sputum or pus on the surface, and by the poured plate method. Anerobic cultures were made on blood agar slants by the Wright method. In sections, the bacteria were stained by the Weigert and Levaditi technic.

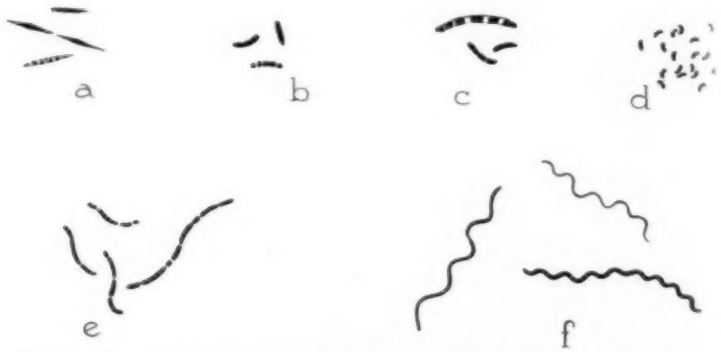

Fig. 16.—Types of fusiform bacilli and spirochetes observed in putrid lesions of the lungs. Similar forms are observed about teeth and tonsils. Typical fusiform, solid and granular (*a*); curved fusiform solid and barred (*b* and *c*); short forms or comma bacilli (*d*); pleomorphic forms seen in cultures (*e*); fine and coarse spirochetes.

The organisms found in the lesions conform, for the most part, in their morphology and cultural characteristics to those describing the teeth and tonsils. The fusiform bacilli appear as typical forms, often barred and slightly curved. Thread like, mycelial like organisms may be pleomorphic forms. The latter never branch, and about them many of the typical bacilli and spirochetes may be grouped. Short fusiform bodies or comma bacilli often are associated. They are gram-negative and non motile (Fig. 16). The spirochetes are actively motile, gram-negative, fine or coarse, forming from four to ten turns, resembling in morphology the forms called *Spirochaeta vincenti, Spirochaeta macrodentium* and microdentium (Fig. 16). The cocci invariably associated with anerobes are gram-positive diplococci, which on culture are most

often *Streptococcus viridans,* occasionally *Streptococcus hemolyticus* and in some instances both. The viridans type may show anerobic properties. In their fermentative properties and pathogenicity for rabbits, these streptococci correspond to those observed about teeth and tonsils. In the majority of instances the before mentioned organisms occur in symbiosis, but in a few either staphylococci, influenza bacilli, leptothrix, *B. capsulatis,* and *Micrococcus catarrhalis* may be found. In fatal cases the *Streptococcus hemolyticus* is most constantly associated with the anerobes.

The mode of infection with these organisms is readily understood where aspiration is a factor. Following general anesthesia, tonsillectomy, perforating lesions, the secretions of the mouth rapidly give rise to pathologic changes in the lung. In the tuberculous lung, or in bronchiectasis the organisms may secure a foothold probably by inhalation of droplets carrying these organisms, first as saprophytes, later producing lesions varying from putrid bronchitis to gangrene. It is possible that in a few instances these bacteria may enter as emboli from a focus and form a metastatic lesion in the lung. Where the spirochetes are found in the lung, such is probably not the route, as in the blood stream the spirochetes apparently are destroyed. In rabbits injected intravenously with mixtures, the spirochetes disappeared while fusiform bacilli and cocci are demonstrable in the pulmonary lesion. Similar findings are encountered in the metastatic putrid brain diseases complicating putrid bronchiectasis.

In the instances where these organisms cause lesions in the normal lung, or at least in a lung where no local predisposing factor is demonstrable, the organisms concerned may be of enhanced virulence or possibly of exogenous origin. Epidemics of Vincent's angina and noma have been described[9] where such exogenous bacteria are responsible. While as yet we have made no observations indicating epidemic fusospirochete pulmonary infection, such epidemic strains may appear in an outbreak of pulmonary infections.

PATHOLOGY

The lesions observed due to these organisms are of a great variety, depending to large extent on the underlying factors, the resistance of the patient, and the behavior of the pathologic process. In all, the tendency to necrosis and the production of a foul smelling lesion are the striking characteristics.

The simplest lesion occurs in the form of a putrid bronchitis. Buday observed such cases at necropsy, in which the necrosis was limited to the mucous membrane, and the lumen was filled with masses of

bacteria and detritus. We have observed similar lesions in the bronchi but associated in all instances with a necrotic process in the lung parenchyma.

A more commonly seen lesion is that of a bronchopneumonic consolidation in any lobe, with formation of a single abscess cavity. In this type the bronchopneumonia surrounding the abscess cavity appears as an interstitial form with intense cellular infiltration at abscess wall. The cavity is covered with shaggy green membrane of fibrin and masses of bacteria. Fusiform bacilli and cocci may form the center of the clumps, while at the periphery the comma bacilli and spirochetes may be abundant. In the membrane the bacilli and cocci appear predominantly; the spirochetes, however, are most numerous at the margin. The cocci extend up through the lymphatics in the alveoli walls and septa. In the more extensive lesions, the bronchopneumonic areas may be confluent, and the areas of necrosis and cavity formation multiple. Occasionally, discrete or lobular forms of bronchopneumonia with central softening is seen (Fig. 3). The distribution of the bacteria resembles that seen in the solitary abscess, but the spirochetes begin to show a tendency to migrate away from the margin of the necrotic wall. The lesions are more gangrenous in character, with green discoloration of the involved areas. These lesions may be seen at necropsy in all stages, acute, subacute, and chronic forms with considerable fibrosis and thickenening of the bronchi.

Of great interest is the diffuse form of gangrene. This lesion represents the result of the action of the anaerobes at their highest pathogenic power. A whole lobe or the entire lung may be involved with multiple cavitations, some of which may become a huge size. The entire lung is discolored green and is very putrid. In the cavities, large sloughs of tissue and fibrin occur. The bronchi and pleura are invariably involved. Microscopically, the consolidation is in the formation of an interstitial pneumonia (Fig. 5). The infiltrating cells are predominantly of the mononuclear types. In the region close to the cavity, the alveoli are filled with fibrin and large numbers of mononuclear cells. At the margin and in the necrotic tissue masses of enormous numbers of bacteria and degenerated polymorphonuclear leukocytes are seen. The spirochetes at the margin appear innumerable, and are seen migrating in great numbers into the neighboring tissue (Figs. 4 and 1 *a*). Cocci are found in the lymphatics and alveoli of the most remote portions.

The blood vessels in the more extensive processes are filled with thrombi, which may be rich in bacteria clumps, made up of fusiform bacilli, spirochetes and cocci. Such thrombi are probably the source of the metastatic lesions in the brain. The bronchi are often filled with necrotic tissue and bacteria. The mucosa may be ulcerated and the

bacteria may be seen extending under the mucosa into the alveoli. The peribronchial lymph glands become enlarged and soft but not necrotic. The pleura frequently is covered with fibrin. Old cases show many fibrous adhesions. The pleural cavity often is typically involved with the formation of a serofibrinous exudate containing streptococci. In the diffuse types of gangrene, a cavity may rupture through the pleura with the production of foul, green pus, containing similar forms of bacteria as in the lung. The pericardium may be involved in a terminal serofibrinous pericarditis.

The other portions of the lung, aside from the gangrenous areas, may be the site of a nongangrenous bronchopneumonia, edema and marked congestion. Tuberculosis of various forms, bronchiectasis (Fig. 7), and carcinoma may be associated as underlying factors. The parenchymatous organs show cloudy swelling in the more acute cases. Of special interest is the occurrence of brain abscess, particularly with putrid bronchiectasis (Fig. 8). The lesion is usually in the parietal lobe. The abscess wall is shaggy and necrotic and reveals fusiform bacilli and cocci but no spirochetes (Fig. 9). The streptococci may extend along the pia into the meninges and give rise to acute meningitis.

It would seem that the streptococcus or other pyogens affect the tissue first, preparing the soil for the growth of the anerobes. The putrid portions correspond to the distribution of the bacilli and spirochetes. The latter advance before the bacilli and may be found in areas of little or no necrosis. The pyogens spread through the lymphatics into the connective tissue, causing interstitial pneumonia in remote portions and serofibrinous pleuritis.

SYMPTOMS

The symptoms are variable, depending on the type of lesion. Acute and chronic forms of fusospirochete infection are to be considered. The foul expectoration, in which the causative organisms are demonstrable, is common to both. Physical signs will depend on the location of the lesion. The course and termination are very inconstant.

ACUTE

Both abscess and gangrene may develop rapidly, particularly after some definite etiologic factor, such as anesthesia or perforation of the bronchi. In the simple abscess, cough sets in, first nonproductive, together with rise in temperature and usually leukocytosis. The lesion softens in from twelve to fourteen days and may drain gradually or rupture suddenly into a bronchus, with the expectoration of foul smelling pus. Physical signs are variable and may be wanting or are sometimes obscured by a moderate effusion on the affected side. The

roentgen ray is of value at this period. A solid shadow with cavity formation, often with fluid level, develops. As the lesion resolves, physical signs become fewer, the cavity smaller, and the density disappears in the roentgen-ray film. Most of the single abscesses terminate favorably, with drop of temperature to normal in from a few days to several weeks, disappearance of expectoration and physical signs of consolidation. In a few, progressive involvement of new areas with the formation of new cavities may occur. After a period free from symptoms, fever and foul expectoration may recur and evidences of consolidation reappear.

The formation of multiple cavities leads to a more severe form and prolonged course of the disease. A septic type of temperature, progressive loss of weight, increasing rapidity of pulse, profuse expectoration of foul sputum may be extended over a period of several weeks or months. In some, only a slight temperature rise with varying amounts of expectoration may be periodic. The physical signs are most extensive, involving most often the lower lobes.

Acute gangrene usually appears with fever, pain in the chest and cough with the development later of very foul breath and putrid liquid green expectoration. The physical findings may show involvement of an entire lobe or lung, with signs usually of large cavitation in the diffuse form of gangrene. The roentgen ray presents diffuse infiltration with cavities and rapid progressive involvement of new areas. The course is generally over a period of two or more weeks, with death from the overwhelming toxemia. In the lobular or bronchopneumonic type of gangrene, the clinical picture is not so severe or progressive, and it develops as a rule into a chronic state which may persist for months. During this stage, periods of improvement, of no fever or of slight expectoration may often alternate with periods of pyrexia, toxemia and foul expectoration.

In bronchiectasis, the ordinary symptoms extend over a period of many years. At various intervals the patient may complain of the foul smelling expectoration and constitutional symptoms. When such symptoms arise, it is often the result of superimposed infection or an extension into the uninvolved tissues by fusiform bacilli, spirochetes, and associated pyogens. Fever of from 100 to 102, foul breath, leukocytosis, from 9,000 to 15,000, usually develop at this time. The sputum may be greatly increased in quantity and is decidedly more putrid and often blood stained. The organisms appear in great numbers. When improvement begins, the odor diminishes and the numbers of bacteria become fewer. One can, however, demonstrate the anerobes in moderate numbers in sputum with no odor. It would appear that the odor results from poor drainage of the cavities and from the necrosis in the walls of the cavities and adjacent tissues. Physical signs are

more diffuse during febrile periods and new cavities may become demonstrable in the more extensive lesions. The roentgen ray is of particular value, revealing fresh infiltrations about the older bronchiectatic cavities, with bronchopneumonic areas in more remote parts which in the more serious infections may become confluent and form new cavitations.

COMPLICATIONS

Extension of infection to the pleura is not uncommon in abscess, gangrene or bronchiectasis. Serofibrinous pleuritis may develop with an effusion which obscures the physical and roentgen-ray signs of lung involvement. In most instances the exudate contains streptococci and has no odor. A more serious complication is the development of putrid empyema or pyopneumothorax, in which conditions similar organisms, as in the sputum, can be demonstrated. As a rule such an exudate results from the direct extension, with rupture of a gangrenous cavity into the pleural cavity.

Bronchopneumonia, with no tendency to softening or gangrene, may occur in the previously uninvolved portions of the same lung or in the opposite lung.

A striking complication, peculiar to the fusospirochete pulmonary infection, is the development of a single or multiple metastatic putrid abscess in the cerebrum, apparently through the blood stream. Focal symptoms, motor and sensory, developing in the course of abscess in bronchiectasis would indicate such involvement. A terminal acute meningitis usually due to the streptococcus may also arise from extension to the meninges.

DIAGNOSIS

The diagnosis of fusospirochete infection depends on the proper examination of the sputum, together with clinical evidences of pulmonary involvement. The sputum should be collected over a period of twenty-four hours. The quantity is variable, but in instances where drainage into bronchi is open, as much as from 300 to 500 c.c., or more, may be collected each day. When specimens are being obtained, the patient should be instructed to brush the teeth several times a day and frequently employ a mouth wash. If these precautions are taken, the anerobes normally about the mouth will be reduced in number and will be less readily mistaken for the same organisms that may occur in the sputum. The odor is variable. At certain stages of abscess and bronchiectasis, the odor may be slight; at other times it becomes foul. In gangrene, it is always very putrid. When profuse in quantity the sputum forms three layers, an upper frothy and mucopurulent, middle transparent and viscid and lower gray or green. In all layers the same organisms can be demonstrated, although in the bottom they may be

more numerous. Examination of a fresh specimen may reveal fatty acid crystals, tissue débris, pus, elastic tissue, and masses of bacteria. To determine the type of bacteria, the sputum should be washed in several dishes of saline solution and smeared on the slide gently in order not to distort the spirochetes. From 5 to 10 per cent. carbolfuchsin for five minutes or the Fontana method for staining spirochetes may be employed. Pleomorphic forms of fusiform bacilli, particularly the ordinary straight, curved and short comma types, together with spirochetes and streptococci are the most common combination of organisms observed (Fig. 16). In several instances, fusiform bacilli with no or very few spirochetes were found. In such, repeated examination may reveal spirochetes. In this connection, it should be emphasized that the absence of spirochetes in the sputum does not eliminate the possibility of their presence in the lung. In the discussion of the bacteriology, it was pointed out that there is often a definite distribution of these bacteria in the tissues with fusiform bacilli, cocci, few spirochetes in the pyogenic membrane, and spirochetes most numerous at the margin of abscess wall. If the fusiform bacilli are numerous in the sputum one can reasonably presume that the symbiotic spirochetes are associated in the pulmonary lesion.

Among the important symptoms the foul breath may be misleading. A similar odor may be detected in diseased tonsils, carious teeth and gingivitis. In these conditions, the same bacteria are generally the underlying cause. In interpreting foul breath as a symptom of pulmonary involvement, the mouth as a source of odor should be eliminated. Physical signs of pulmonary involvement are variable owing to the extent of the lesion and the frequency of involvement near the hilum. Often the findings are few or indefinite, yet in the roentgen-ray film an abscess of considerable size may be clearly demonstrated. Fluid in the pleural cavity may obscure the findings in the underlying lung.

In differential diagnosis the pulmonary conditions due to other spirochetal infections should be considered. Castellani [10] described the spirocheta bronchialis occurring in pulmonary hemoptysis chiefly in the tropics. The expectoration is thin, odorless, watery and often a vivid pink color. The spirochetes, according to Fantham,[11] differ from Vincent's types. They are more actively motile, die more quickly, stain less readily, and produce coccoid bodies. The Wassermann reaction is negative, blood count normal, and physical and roentgen-ray signs very scant.[12] The condition responds well to sodium cacodylate and neo-arsphenamin and leads to rapid recovery. Apparently in typical

10. Castellani, A., and Chalmers, A. J.: J. Trop. Med. **22**:1882-1886, 1919.
11. Fantham: Ann. Trop. Med. & Parasitol. **9**:391-412, 1915.
12. Violle, H.: Presse méd. **39**:359-361, 1918.

acute cases, the pulmonary infection is due to the specific spirochetes of Castellani, but the more chronic types that have been described as due to the same spirochetes are erroneously reported, resembling more the fusospirochete type of pulmonary involvement that we have encountered. Confusion may arise if only spirochetes are sought for in the sputum; in our series we have never failed to find fusiform bacilli when spirochetes occurred.

Pulmonary syphilis has been reported in patients presenting solid shadows in the roentgen-ray film of the chest, a positive Wassermann and clearance under arsphenamin therapy. In an analysis of such reports, the clinical picture is frequently one of suppuration and gangrene. In our own experience, we have not observed solid lesions or gummas in the lung, even in individuals with positive evidence of syphilis in other viscera. In fusospirochete infection, the Wassermann is negative. In one instance, a positive Wassermann was obtained, but the syphilis in this patient was coincident. Furthermore, fusospirochete infection appears to respond readily to arsenic therapy. From our studies, we believe that the interpretation of pulmonary syphilis has been based on evidence that points to a lesion often due to fusospirochete infection.

Not all pulmonary conditions with foul sputum are due to the fusospirochetes. We have observed intensely foul expectoration in a patient with tuberculosis and secondary infection with *B. pyocyaneus*, another in which a small gram-negative anerobic bacillus was obtained in cultures at necropsy. Foul smelling abscesses of the lung have been encountered from which colon bacilli were isolated in a patient with pelvic peritonitis. Such organisms causing foul lesions in the lung are exceptional, but should be considered where the fusospirochetes are not demonstrable.

In all patients with putrid expectoration, possible underlying predisposing lesions should be investigated. Tuberculosis, carcinoma, or foreign bodies may be overlooked if the sputum and foul expectoration alone are considered. Physical and roentgen-ray examination may reveal such associated pathologic changes. The error made is often the reverse; that is, to recognize the tuberculosis, or foreign body and to disregard the possible complication of abscess or gangrene which may be the more serious condition.

The course and duration of fusospirochete infection is extremely variable. The acute abscess may rupture in two or three weeks suddenly into the bronchus with profuse expectoration for a day, with rapid recovery. Some drain more slowly but disappear spontaneously in from two to four weeks. A considerable number become chronic with periods of improvement and recurrence of symptoms. Multiple abscess formations are less favorable and may rapidly terminate fatally or develop into

a chronic state. Gangrene may be fatal within a period of from two to four weeks, or become a chronic condition lasting many months, with an unfavorable outcome.

Bronchiectasis complicated by fusospirochete infection behaves irregularly. In some, the putrid expectoration is constantly present, while in others it appears for a few weeks at intervals of months or years. In the interval profuse odorless expectoration often persists, and in the sputum the anerobes can still be demonstrated. In both bronchiectasis and chronic abscess formations, these organisms apparently persist as opportunists in the cavitations or tissues, and under certain conditions become pathogenic with the development of recurrences of symptoms of fever, foul expectoration and signs of consolidation.

The prevention of pulmonary abscess and gangrene will depend to a considerable extent on the elimination of sources of infection. It is, of course, impossible to remove completely the fusiform bacilli and spirochetes from the oral cavity, but much can be done to reduce the number of such organisms. The teeth should be free of excessive tartar deposits. Pus pockets, carious teeth, pyorrhea, in which conditions these bacteria occur in great abundance should be properly treated. Tonsils in which masses of these organisms are prone to accumulate are best removed. In some, expression can be employed. Such procedures are especially indicated in the patient about to undergo anesthesia tonsillectomy, and in patients with chronic bronchitis, bronchiectasis or pulmonary tuberculosis.

TREATMENT

Arsenic, particularly arsphenamin has been employed in fusospirochete infection of the mouth. In stubborn cases of Vincent's angina, good results have been obtained. Plaut [13] extended its use in stomatitis and in pulmonary gangrene. Gerber [14] reported its use locally in Vincent's angina and gingivitis. Peemöller [15] reported one case of fusospirochete pulmonary gangrene treated successfully with arsphenamin, and reviewed eight cases of gangrene treated similarly by Hirsch, Weiss and others.

Our experience has shown favorable results with neo-arsphenamin in pulmonary abscess; from 0.3 to 0.9 gm. was administered once a week. It is, of course, recognized that abscesses frequently heal spontaneously when the drainage is good. However, the improvement in several instances definitely followed the medication. In Case 9 no treatment was given for five weeks. The clinical and roentgen-ray findings

13. Plaut, H. C.: Deutsch. med. Wchnschr. **3**:117, 1914.
14. Gerber: Deutsch. med. Wchnschr. **45**:913, 1919.
15. Peemöller, F.: Deutsch. med. Wchnschr. **48**:680 (May 26) 1922.

indicated that the lesion had not improved but had even extended into the periphery. The introduction of neo-arsphenamin directly improved his condition, and in four weeks the fever disappeared and physical and roentgen-ray examinations demonstrated considerable resolution in the lesion. In Case 1 the patient was becoming progressively worse, although she was expectorating foul sputum (Fig. 1). The temperature just before treatment was 103. A single dose of neo-arsphenamin was followed by quick improvement, normal temperature three days later, less expectoration and complete clearance of the lesion occurred in three weeks (Fig. 2). The more chronic types did not respond as readily, and some showed no definite change.

In bronchiectasis, the therapy can only influence the complicating infection by the anerobes, and prevent possibly the formation of new cavitations. Distinct improvement with disappearance of foul smell of sputum, less fever and clearance of lesions was observed, but the cavities, of course, remained. No permanent results can be expected for this reason. Patients returning with recurrence of the symptoms require additional treatment.

In gangrene, we have not had the opportunity of treating early cases. In the far advanced stage the neo-arsphenamin apparently for a time caused diminished expectoration and some favorable changes in constitutional symptoms, but the toxemia ultimately overwhelmed the patient. It is evident that to obtain recovery in gangrene, the disease must be treated early. We are of opinion that a patient with pulmonary abscess and gangrene should have the benefit of arsenical treatment before more radical procedures such as pneumothorax and surgery are instituted. When surgery is necessary, arsphenamin should be combined in the treatment.

SUMMARY

1. Thirty-seven cases of pulmonary infection due to certain anerobes, characterized by abscess formation and gangrene, are reported. The bacteriologic, pathologic, and clinical studies indicate a type of infection which may be classified as a distinct clinical entity. We refer to the process as a fusospirochete pneumonia, but pyogens, particularly streptococci, play an important contributory rôle.

2. The lesion is largely in the form of simple or multiple abscesses, gangrenous bronchopneumonia or a diffuse form of gangrene. The development of this type of infection depends to a great extent on predisposing factors such as general anesthesia, tonsillectomy, aspiration of foreign bodies, perforating lesions into the trachea and bronchi, infections, especially pneumonia, carcinoma, tuberculosis, and bronchiectasis and circulatory disturbances of various kinds. In a few the lesions develop without evident predisposing causes.

3. The clinical picture and course is variably influenced largely by the underlying contributory factors, resistance of the patient, and the extent of the lesion.

4. Probably in all cases the sources of infection relate back to the teeth and tonsils where the fusiform bacilli and spirochetes and cocci are present in enormous numbers. The prevention of these pulmonary infections, therefore, lies in the proper hygiene of the mouth.

5. Arsenic, particularly neo-arsphenamin, has a definitely therapeutic action on fusospirochete infection. Most favorable results are obtained in the early cases.

THE EFFECT OF IODIN IN EXOPHTHALMIC GOITER*

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At a meeting of the Association of American Physicians in May, 1923, Plummer [1] reported on the use of iodin (compound solution of iodin) in the treatment of exophthalmic goiter. Iodin has been used in this disease by many in the past but has for the most part fallen into disrepute. Plummer, however, claimed striking benefit from its use. Following this suggestion we began shortly afterward the investigation which is reported in this paper. It is a continuation of the studies of various forms of therapy in exophthalmic goiter that have been made during the last ten years at the Massachusetts General Hospital.[2] Our results seem to be similar to those obtained in the Mayo Clinic, which have been recently published by Plummer and Boothby.[3]

The chief effect is what may be called the iodin remission. Trousseau,[4] in 1863, achieved this same result when he inadvertently gave a patient with exophthalmic goiter tincture of iodin in place of tincture of digitalis. He says: "In the course of October, 1863, I was consulted by a young married lady, who habitually resides in Paris. She was suffering from subacute exophthalmic goiter. The bronchocele was of great size. When I examined her for the first time, although I had let her rest for a long while, and although I repeated the examination several times, and at sufficiently distant intervals, so as to make sure

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* This article is No. 29 in a series of studies in metabolism from the Harvard Medical School and allied hospitals. The expenses of this investigation have been defrayed, in part, by a grant from the Proctor Fund of the Harvard Medical school for the Study of Chronic Diseases.

1. Plummer, H. S.: Results of Administering Iodin to Patients Having Exophthalmic Goiter, J. A. M. A. **80**:1955 (June 30) 1923.

2. Means, J. H., and Aub, J. C.: A Study of Exophthalmic Goiter from the Point of View of the Basal Metabolism, J. A. M. A. **69**:33 (July 7) 1917. Means, J. H., and Holmes, G. W.: Further Observations on the Roentgen-Ray Treatment of Toxic Goiter, Arch. Int. Med. **31**:303 (March) 1923. Richardson, E. P.: Relative Value of Surgery and Roentgen Ray in the Treatment of Hyperthyroidism, J. A. M. A. **80**:820-825 (March 24) 1923. Segall, N. H., and Means, J. H.: The Immediate Effect of Subtotal Thyroidectomy in Toxic Goiter, Arch. Surg. **8**:176-187 (Jan.) 1924.

3. Plummer, H. S., and Boothby, W. M.: The Value of Iodin in Exophthalmic Goiter, J. Iowa M. Soc. **14**:66 (Feb.) 1924.

4. Trousseau: Clinical Lectures, Vol. 1, p. 587, Translation by P. V. Bazire, London, The New Syndenham Society, 1868.

that she was no longer under the influence of emotion, I still found her heart beat at the rate of 140 to 150 times in the minute. I recommended hydropathy and I wished to administer at the same time tincture of digitalis, but preoccupied with the idea that there would be some danger in giving iodin, I wrote iodin instead of digitalis, so that the patient took from 15 to 20 drops of tincture of iodin a day for a fortnight. When she then came back to me, her pulse was only 90. I found out my mistake, and I substituted tincture of digitalis for that of iodin, but, after another fortnight, the pulse had again gone up to 150, so that I at once returned to the iodin." This behavior of the pulse in exophthalmic goiter (and of the basal metabolic rate also, as we now know), has been frequently observed during the last year exactly under iodin as it was by Trousseau sixty years ago.

CASES STUDIED

Since May, 1923, forty-two cases of exophthalmic goiter have been treated with iodin, as compound solution of iodin, at the Massachusetts General Hospital. Of these, seventeen were outpatients, who reported frequently to the metabolism laboratory to be observed. The conditions under which they were followed were, of course, less uniform than those of the patients who were in the hospital. Of the latter, there were twenty-five. These patients were kept in bed continuously. Most of them were being prepared for operation. No patient of either group was considered to have adenomatous goiter with hyperthyroidism. Some did not have exophthalmos, but in these the symptoms were still thought to be due to what is termed "toxic hyperplasia," and this diagnosis was confirmed anatomically after operation.

ADMINISTRATION OF IODIN

Liquor Iodi Compositus, U. S. P., has a most objectionable taste, but all of the patients soon became accustomed to taking it by mouth. In no case was it necessary to give it per rectum as Plummer and Boothby have done in some emergencies. It was given after meals, well diluted with water. The mouth was rinsed at once after taking. The usual dose by mouth was 15 drops daily. Forty-five drops a day has been tried in two cases, but is apparently not much more effective than 15. The problem of the quantity of the dose in relation to various factors, such as the size of the gland, rate of metabolism, age of the patient, pathology of the goiter, duration of the disease, and the sympathomimetic symptoms, is yet to be solved. The parenteric routes of administration have not been studied. We gave one patient a solution [5] of iodin in mineral oil without potassium iodid and the result was

5. Devised by Dr. James L. Stoddard.

similar to those obtained with compound solution of iodin. The duration of medication has been from ten days to six months in individual cases.

METHODS

The effects of treatment were followed by determinations of basal metabolic rate, pulse and weight. The Roth-Benedict apparatus was used. Precautions for preserving or producing basal metabolic conditions were taken.

ANALYSIS OF DATA

An abrupt remission of the disease, evidenced by fall of metabolic and pulse rates, increase of weight, and diminution of symptoms was the immediate result of the administration of iodin in more than 80 per cent. of our patients. This remission was most likely to occur in those patients who were resting in bed in the hospital without marked

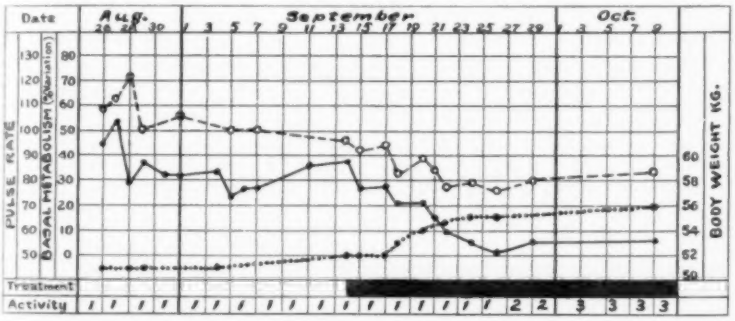

Chart 1.—Typical iodin remission in exophthalmic goiter. Solid line is basal metabolic rate in percentage variation above normal which is 0. Dash line is pulse rate per minute. Dotted line is weight in kilograms shown at right. Activity 1 is complete rest in bed; 2 is partial rest; 3 is usual mode of life. From August 26 to September 14 no treatment but rest in bed was given. On September 14 compound solution of iodin, 15 minims daily, was begun and given thereafter daily, as indicated by the solid black in the treatment space.

physical or psychic complications. It did occur, however, in outpatients, but was then less rapid and less marked.

The findings in a patient who had a typical abrupt remission are shown in Chart 1. The history is as follows:

REPORT OF CASE

M. M., a woman, aged 23, first noted fatigue, nervousness, palpitation, dyspnea, diarrhea, and tremor in September, 1922. The goiter was perceptible in the following Spring. She entered the Massachusetts General Hospital in August, 1923, with exophthalmos, lagging lid, a diffuse symmetrical goiter which had a thrill and bruit, a moist skin, tremor and tachycardia, and a basal metabolic rate of plus 45 per cent., pulse rate of 110 per minute, and weight

51.5 kg. The patient remained at complete rest in bed in the hospital for one month. After three days the basal metabolic rate was plus 38 per cent. Two weeks later, without any medication, the rate was again plus 38 per cent., pulse rate 95, weight 52 kg. This period of two weeks forms an excellent control period. Fifteen minims of compound solution of iodin was now given by mouth daily. No other change in treatment was made. During the next twelve days the basal metabolic rate rapidly decreased until it reached plus 1 per cent., the pulse rate became 78 per minute and the weight increased to 55 kg. The patient appeared much quieter with less exophthalmos and tremor. She said she felt well.

Remissions of this character were frequently as rapid and as extensive as those which follow subtotal thyroidectomy. Chart 2 shows the daily basal metabolic rate curves of eight patients. There is a control period of five days. The points at which daily iodin administration

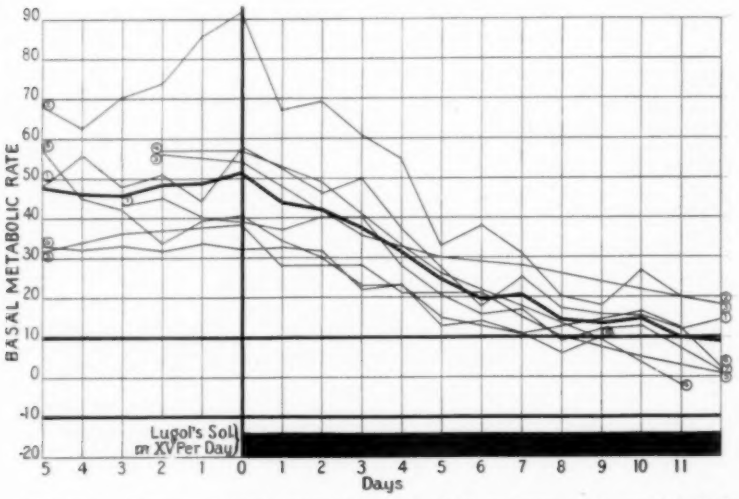

Chart 2.—Curves of basal metabolism of eight patients with exophthalmic goiter given iodin daily, beginning with zero line. Average curve, solid black double width.

was started are plotted on the zero line. The basal metabolic rates in all these cases decreased rapidly during the next ten days. The line representing the average of this group is double width. On the day of beginning iodin treatment it is at a level of plus 51 per cent. On the tenth day afterward it is at plus 14 per cent. This gives an average rate of detoxication of about 3.7 points daily. This is nearly the same rate of detoxication that Segall and Means [2] found after subtotal thyroidectomy. By daily metabolic rate measurements of patients before and after operation, they determined accurately that the rate of detoxication is about 3.7 points a day. The average curve of their group of

eleven is at plus 45 per cent. the morning before operation. During the next ten days after a postoperative peak, it falls rapidly to plus 8 per cent. It is a most important theoretical and practical fact that compound solution of iodin will have in many cases of exophthalmic

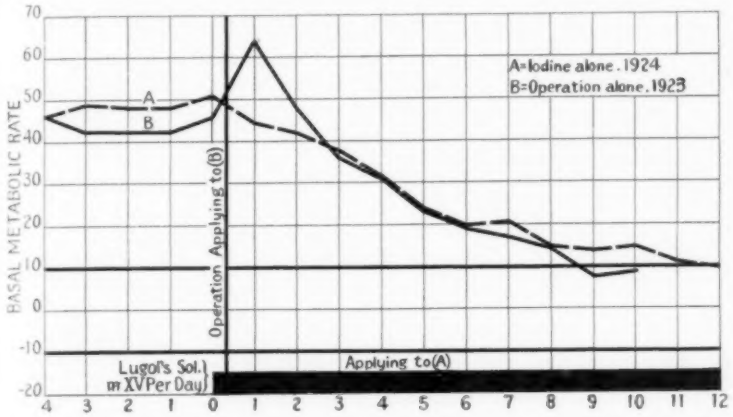

Chart 3.—The average curve obtained by Segall and Means showing effect of subtotal thyroidectomy is a continuous line; the average curve showing the effect of iodin alone (Chart 2) is an interrupted line. Note the absence of the postoperative peak in the latter curve, but that otherwise the curves are nearly superimposed.

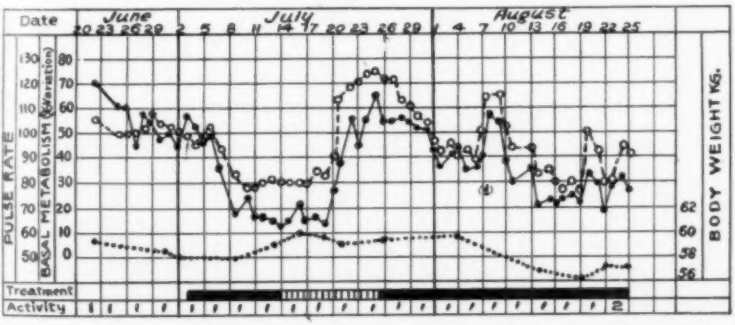

Chart 4.—Repeated iodin remission. Solid line, metabolism. Dash line, pulse. Dotted line, weight. Treatment was rest until solid black band, indicating compound solution of iodin, 15 minims per day. Placebo indicated by cross bars, from July 14 to 25, during which time there was abrupt recurrence. Iodin restarted. (1) indicates hemithyroidectomy. Activity 1 is rest in bed.

goiter (48 per cent. of our series) the same immediate effect on metabolic rate as removing five-sixths of the gland. The average curves of the effects of iodin and of operation are charted together (Chart 3) to emphasize their similarity.

The demonstration of iodin as the causal agent of this remission, we think, is completed by the fact that substitution of a placebo during the remission is followed by abrupt recurrence, and in addition, that if iodin is again started a second remission is produced. We have observed this in four cases, two of which are illustrated in Charts 4 and 5.

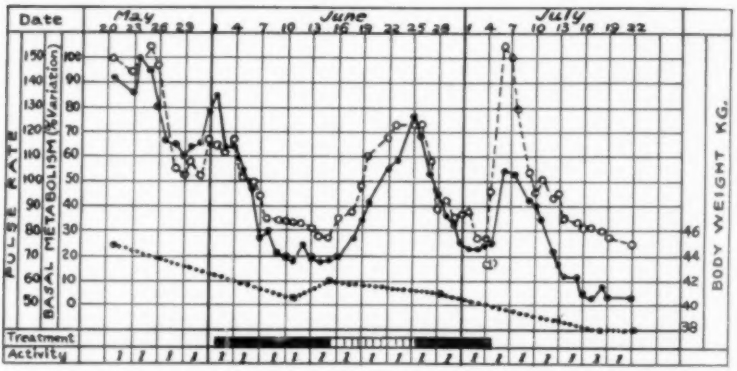

Chart. 5.—Repeated iodin remission. Black band in treatment is iodin, cross bars, placebo. (1) is subtotal thyroidectomy.

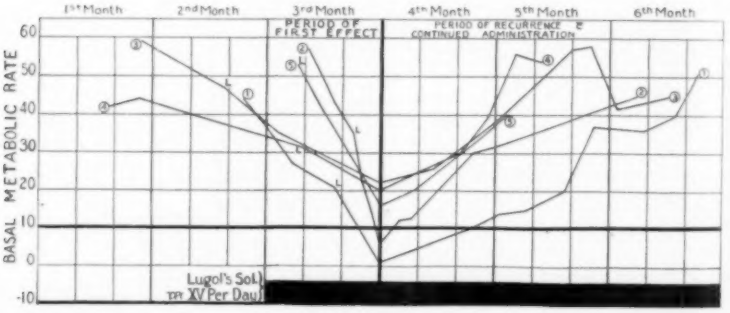

Chart 6.—Remission and recurrence under iodin. Five metabolism curves remission shown by fall of metabolic rate to the central ordinate. Compound solution of iodin started in the individual cases at L. Recurrence shown by rise of the metabolism curves during succeeding three months.

That such a remission is not maintained by continued administration of iodin when the patient returns to daily life is shown in the continuation of the history of M. M., described in the foregoing.

One week after reaching a normal level of basal metabolism the patient returned to her studies as a senior in college. A month after this, although taking iodin every day, the basal metabolic rate was plus 13 per cent., pulse 95, weight 56 kg. Toward the end of the second month the basal metabolic rate

was plus 30 per cent., pulse 100, weight 56 kg. Toward the end of the third month, the basal metabolic rate was plus 52 per cent., pulse 117, weight 56 kg.

A similar prolonged recurrence was observed in four other patients also taking 15 minims of compound solution of iodin daily for from two to four months. Chart 6 shows the curves of these five patients. The lowest points, indicating the initial effect of iodin, are synchronized. The subsequent recurrence with continued iodin administration is well

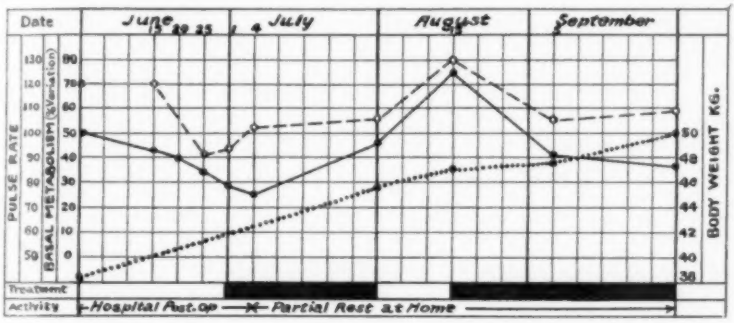

Chart 7.—Post-iodin reaction. Metabolic rate, solid line; pulse rate, dash line; weight, dotted line. Iodin indicated by solid band in treatment space is compound solution of iron, 15 minims per day; given from June 29 to August 1; omitted from August 1 to 15; restarted on August 15.

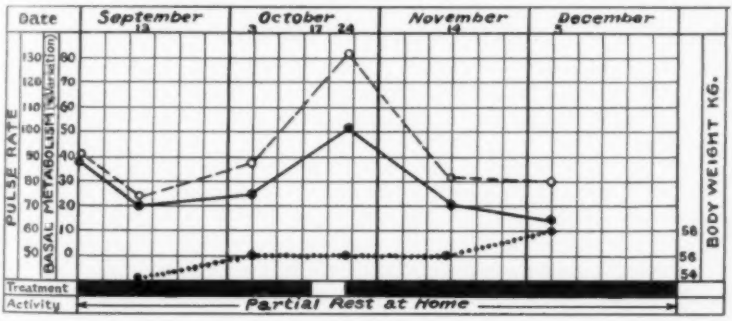

Chart 8.—Post-iodin reaction. Iodin omitted by patient from October 17 to 24.

shown. They reach their original levels in from one to two months. None of these patients were resting in bed. The dosage throughout was unchanged. It is to be noted that there is no period of uniform level of metabolism during this remission. The recurrence begins at once; its rapidity is variable, and the period within normal limits may be very brief, amounting to only a few days, so that if operation is contemplated action must be taken at once while the primary effect of

iodin is predominant. Because of this recurrence under iodin, we believe that as now used iodin is not a cure for exophthalmic goiter, and that it should not be used with this expectation.

The way in which iodin produces this remission in exophthalmic goiter is far from clear. Plummer's [1] theory, that it lies in the iodizing of abnormal thyroxin, is not entirely convincing. For one thing it should be noticed that the dose of iodin given is relatively very great,

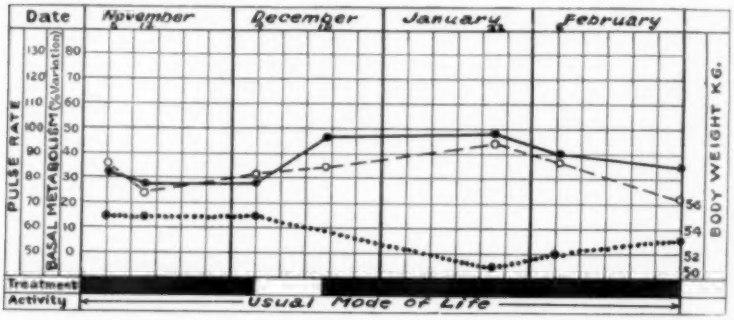

Chart 9.—Post-iodin reaction. Iodin ineffective during November; omitted December 4; restarted December 18.

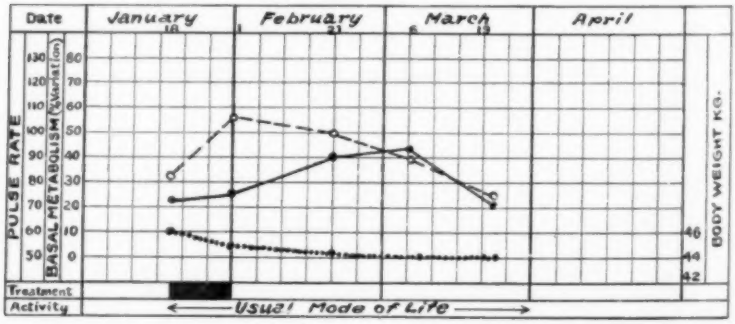

Chart 10.—Post-iodin reaction. Iodin given January 18 to February 1, followed by rise of metabolic rate to plus forty with subsequent return in March to its previous level about plus twenty.

fifteen minims of compound solution of iodin is equivalent to 125 mg. of iodin. The amount of thyroxin iodin necessary to keep the body at a basal metabolic rate of plus 50 is only 2 mg. daily,[6] yet doses smaller than 15 minims a day of compound solution of iodin are not as effective. In addition, we have observed (Chart 6) recurrence of the

6. Plummer, H. S.: Interrelationship of Function of the Thyroid Gland, J. A. M. A. **77**:243 (July 23) 1921.

original disease while the patient was taking this dose, which is enormous when compared with the amount of iodin needed for thyroxin.

After a patient with exophthalmic goiter has been taking iodin, we have found that a rapid rise of metabolic rate and increase of toxic symptoms occur if the iodin is omitted. And this happens whether or not this omission takes place while the iodin is producing its first effect or during the secondary recurrence with continued administration. Illustrations of the former have been shown in Charts 4 and 5. Illustrations of the latter are given in Charts 7, 8, 9 and 10. In Chart 7 it will be noted that the metabolic rate is apparently increasing in spite of the iodin, yet when it is discontinued a still more rapid rate soon is found, but when the iodin is again given, a rate at the former level is subsequently reached. This brings out the very important practical

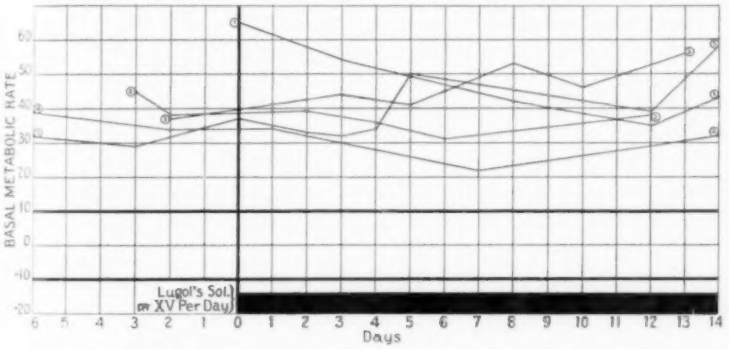

Chart 11.—Metabolism curves of five patients with exophthalmic goiter, in which iodin was without observable effect. All patients resting in bed. Compare with Chart 2.

point if iodin is used as preoperative preparation, whether it is successful or not, no gap between medication and operation should be allowed to occur. We have observed this further sudden increase on discontinuance of the iodin in many instances.

In this connection it is of interest that previous iodinization in no way prevents the toxic effect of thyroxin. This has been shown in rabbits by Sturgis.[7] In human beings it has been found by one of us (HLS) that the taking of iodin in no way reduces the thyrotoxicosis induced by thyroid ingestion, nor accelerates the rate of recovery therefrom.

Some of our patients showing exophthalmos, and in which a hyperplastic thyroid was later found at operation, did not show the iodin remission. A chart (Chart 11) of the metabolism curves of five such

7. Dr. C. C. Sturgis, Boston. Personal communication.

patients is shown. They were all in the hospital under identically the same conditions as those illustrated in Charts 1, 2, 4 and 5, and were given the same dosage of iodin for a period which in the others produced marked effects. It is to be noted that these curves remain practically horizontal and form a control group as to the rest factor, which might have accounted for some of the drop in the first cases cited. The pathologic reports of the cases of this unsuccessful group all show follicular hyperplasia without adenomas. No criterion for accurately differentiating this unsuccessful group from the successful has been found.

As to the probability with which a successful result with iodin is to be expected, it is of course impossible to make anything but a rough approximation from such a small number of cases. The number which we have studied which were treated identically is twenty-five. Of these we have pathologic reports on the thyroid gland in all but two cases. The reports indicate the absence of adenoma and the presence of generalized follicular hyperplasia. Of these twenty-five cases, twenty (80 per cent.) responded to iodin by a more or less extensive remission of the disease. Of these twenty, twelve (48 per cent.) responded with the acute iodin remission resembling the effect produced by subtotal thyroidectomy. In the remaining eight (32 per cent.) the remission occurred, but was less extensive. In five unsuccessful cases (20 per cent.) two of the patients were pregnant and one had cardiac decompensation. If these are omitted from the calculation, iodin administration was successful in twenty of twenty-three, or 92 per cent. of our hospital cases.

CONCLUSIONS

1. Iodin by mouth will produce abrupt remission in most cases of exophthalmic goiter.

2. The remission is often as rapid and as extensive as that following subtotal thyroidectomy.

3. It is believed that iodin is the causal agent of this remission.

4. Iodin alone as now used has not been shown to be sufficient to suppress the disease permanently.

5. After a patient with exophthalmic goiter has been taking iodin, a rapid rise of metabolic rate and increase of toxic symptoms will occur within one or two weeks if the iodin is stopped.

6. In some cases of exophthalmic goiter, iodin has no observable effect

A QUANTITATIVE INDEX OF KIDNEY FUNCTION

THERMODYNAMIC CONSIDERATIONS IN THE ESTIMATION OF RENAL EFFICIENCY *

I. M. RABINOWITCH, M.D.
MONTREAL

From the numerous data available, the deduction is that the chief function of the kidneys is to keep the composition of the blood constant. The kidneys must react to the various deviations from the normal composition of the blood by excreting water or substances dissolved in it. During the process of excretion work is done. All tests for renal efficiency are based on the ability of the kidneys to do their work. It is generally recognized that, since the complete mechanism of the secretion of urine is imperfectly understood, the total work done by the kidneys during this process cannot be accurately determined. Attempts have been made to estimate this work according to known physical principles. Of special note are the procedures of Dresser, Galeotti and Hill. The data thus obtained and some of the renal function tests now in use have been reviewed.[1]

In a recent communication [2] a study was made of the value of the "urea concentration factor" in the estimation of renal efficiency. It was demonstrated that, at least so far as lesions associated with defective excretion of urea are concerned, the urea concentration factor, if determined under a uniform set of conditions described, is a more sensitive test for the detection of impairment in function than the other methods in common use. Further clinical experience with this test, employed routinely in practically all patients having an albuminuria admitted to the Montreal General Hospital has strengthened this view. So far, 610 observations have been made on 284 patients. The results are briefly recorded in Table 1. The blood urea was the least sensitive in the detection of early renal inefficiency, having been found increased in 341 or only 56 per cent. of the total number of observations. The urine urea concentration test [3] was a better index than the blood urea. The "urea concentration factor" was the most sensitive, showing impair-

* From the Department of Metabolism of the Montreal General Hospital. This work was done with the aid of a grant from the Cooper Memorial Fund.

1. Cushny, A. R.: The Secretion of Urine. Monographs on Physiology, New York, Longmans, Green & Company, 1917.

2. Rabinowitch, I. M.: The Urea Concentration Factor in the Estimation of Renal Efficiency, Arch. Int. Med. **32**:927 (Dec. 1923.)

3. MacLean, H., and de Wesselow, O. L. V.: On the Testing of Renal Efficiency with Observations on the Urea Coefficient, Brit. J. Exper. Pathol. **1**:53 (Feb.) 1920.

ment in 573 or 94 per cent. of all the observations. The reason for this appears obvious. The earliest evidence of impaired function may be a diminution in the ability of the kidneys to concentrate. But during a day, by constant effort, the total end products of protein metabolism may be eliminated. Under these conditions the concentration of urea in the blood, the following morning in the post absorptive state, may be normal. The urine urea concentration test would thus be more sensitive than the blood urea. The reasons for the "urea concentration factor" being the most sensitive have been discussed in the previous paper.[2]

TABLE 1.—*Results of 610 Observations on 284 Patients*

Test	No. of Cases	Per Cent.
Blood urea nitrogen increased	341	56
Urine urea concentration diminished	453	76
Urea concentration factor lowered	573	94

Briefly, the urea concentration factor is obtained as follows: No food nor fluids are allowed after six o'clock the evening before the test. At six o'clock the morning of the test the patient voids. This specimen is discarded. Fifteen grams of urea, dissolved in 150 c.c. water, are then given orally. No flood nor fluids are allowed during the test. Blood is collected for analysis before and two hours after, and the urine one and two hours after the administration of the urea. Urea determinations were made on the blood and urine by the Van Slyke (urease) method. All determinations were made in duplicate. The urea concentration factor is represented by the formula

$$\text{U. C. F.} = \frac{\text{Milligrams urea per 100 c.c. urine}}{\text{Milligrams urea per 100 c.c. blood}}$$

The choice of the blood and urine at the stated periods was, as noted by the author of the test,[4] purely arbitrary. The value of urea studies in the estimation of renal efficiency was pointed out in the discussion of the physiologic aspects of urea.[2]

However, as with the other tests in use, the urea concentration factor appeared to yield results of a qualitative nature only. Judging from the clinical picture, since the normal value for the factor was found to be approximately 40, because a factor of 20 was found, it did not appear that the efficiency of the kidneys could be regarded as being only 50 per cent. of the normal.

The object of this communication is to present what appears to be a still more exact method of studying renal function, in that, at least so far as the excretion of one substance is concerned, namely urea, an attempt is made to express the results in quantitative terms. The "urea

4. Harrison, G. A.: On Urea Tests of Renal Function, Brit. J. Exper. Path. **3**:28 (Feb.) 1922.

concentration factor" forms an essential part of the necessary data. It can be shown, mathematically, that considered from another point of view, the factor is, indirectly, a quantitative index, and also what appeared to be a purely arbitrary choice, that is, the periodic collection of the blood and urine, has a real basis. Because of the quantitative nature of the results the clinical value of this test is greatly enhanced. In the evaluation of any laboratory test for clinical use, clinical experience must be the final source of judgment. As in the physical sciences, if experience does not correspond to the deductions of a mathematical expression, either the reasoning is wrong or certain variables enter into the problem not recognized and therefore have been neglected. Experience so far with this test shows that the results obtained parallel more closely the clinical progress of the patient than the other tests in use. The basis of the test is the estimation of the work done by the kidneys, in the excretion of a definite amount of urea, by the application of certain elementary laws of thermodynamics. These will now be briefly considered.

BASIS OF THE TEST

The work done by a gas in expanding isothermally (that is, expansion at constant temperature) by a definite amount from a volume V_1 to V_2 is expressed by the equation $W = R\ T\ \text{Log}_e \frac{V_2}{V_1}$ or $W = 2.3\ R.\ T\ \text{Log}_{10} \frac{V_2}{V_1}$ where W is the work done, R is the universal gas constant, and T is the absolute temperature. The numerical value for R is found from the general gas equation $PV = RT$. That is, $R = \frac{PV}{T}$, and depends on the units in terms of which P and V are expressed. For our present consideration P is expressed in terms of dynes per square centimeter and V in terms of cubic centimeters, R has therefore a value of 0.85 and W is thus expressed in terms of kilogram-meters. The fundamental importance of this equation is generally recognized in biologic studies, since it may be applied to solutions as well as gases.

We are now concerned with the work done by the kidneys in the excretion of a definite amount of urea, and changing the concentration of urea from that in which it exists in the blood to that in which it exists in the urine. By applying the foregoing formula, the work done by the kidneys is calculated as follows:

$$W = 2.3\ R\ T \left[\text{Log}_{10} \frac{C_1}{C_2} + \text{Log}_{10} \frac{C_2}{C_1} \right] \frac{m}{M}$$

Where W = kilogram-meters work
R = 0.85
T = 310 (273 + 37)
C_1 = concentration of urea in the urine before giving the urea
C_2 = concentration of urea in the urine after giving the urea
C_3 = arithmetical mean of blood urea concentration before and after giving urea
m = grams urea excreted during period of observation
M = weight of one gram-molecule of urea (60)

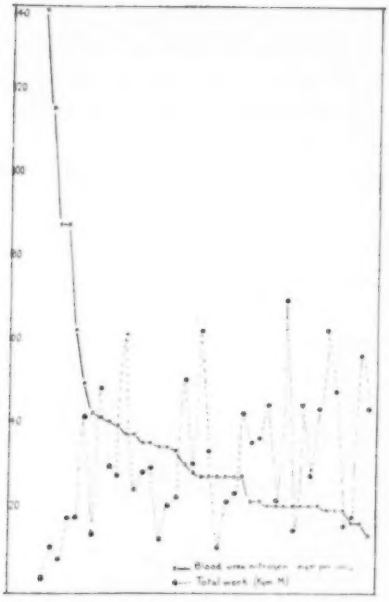

Chart 1.—The relation between the blood urea nitrogen and total work done in two hours.

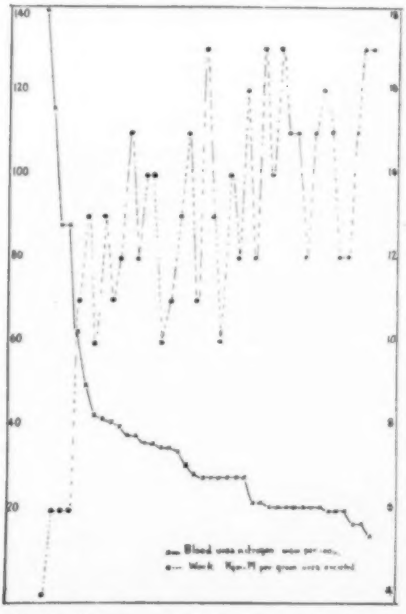

Chart 2.—The relation between the blood urea nitrogen and the work done per gram of urea excreted.

By reducing the formula to simpler terms, not only the application of the factor becomes apparent, but also the idea that the choice of the periodic collection of the blood and urine specimen is arbitrary is dispelled. Thus:

$$W = 2.3\ R\ T\ \text{Log}_{10} \left[\frac{C_1}{C_2} \frac{C_2}{C_1} \right] \frac{m}{M}$$

$$= 2.3\ R\ T\ \text{Log}_{10} \left[\frac{C_2}{C_2} \right] \frac{m}{M}$$

It will be noted that $\left[\frac{C_2}{C_2} \right]$ is the urea concentration factor.

An example of the complete data involved in such a calculation is given in Table 2. These data were obtained from a normal person. It will be noted that the urea concentration factor is obtained in a slightly different manner from that previously described. The value of the arithmetical mean of the concentration of urea of both blood specimens is employed, instead of the one blood only. This procedure increases the value of the factor for normal persons from that of 40, previously recorded, to 50.

TABLE 2.—*Calculation of Work Done in the Excretion of Urea in a Normal Subject*

	Urine			Blood Urea-Nitrogen, Mg. per 100 C.c.		Work	
Hour	C.c.	Urea, per Cent.	Urea, Gm.		Factor	Total Kilogram-meter	Kilogram-meter per Gm. Urea
1	75	3.08	2.31	21	....	....	....
2	60	2.98	1.80	35	49.7	70.4	17.1
Total.....			4.11	Aver. 28			

Under the uniform set of conditions described, a normal person excretes approximately from 3 to 5 gm. of urea in two hours and the kidneys perform in this process from 50 to 85 kilogram-meters work, depending on the amount of urea excreted. But the work done per gram of urea excreted is remarkably constant, approximately 17 kilogram-meters. The importance of recognizing the variations due to the rate of absorption of the urea from the alimentary tract will be shown in the comment of the results.

Observations were made on patients showing an albuminuria. No selection of the cases was made clinically. The subjects included mild and advanced cardiac, renal, cardiorenal, surgical and urologic patients. These are shown in Table 3, which contains the data of the first 40 observations. Further tabulation seemed unnecessary. Chart 1 represents, graphically, the relation between the blood urea nitrogen and total work done in two hours. Chart 2 represents, graphically, the relation between the blood urea nitrogen and the work done per gram

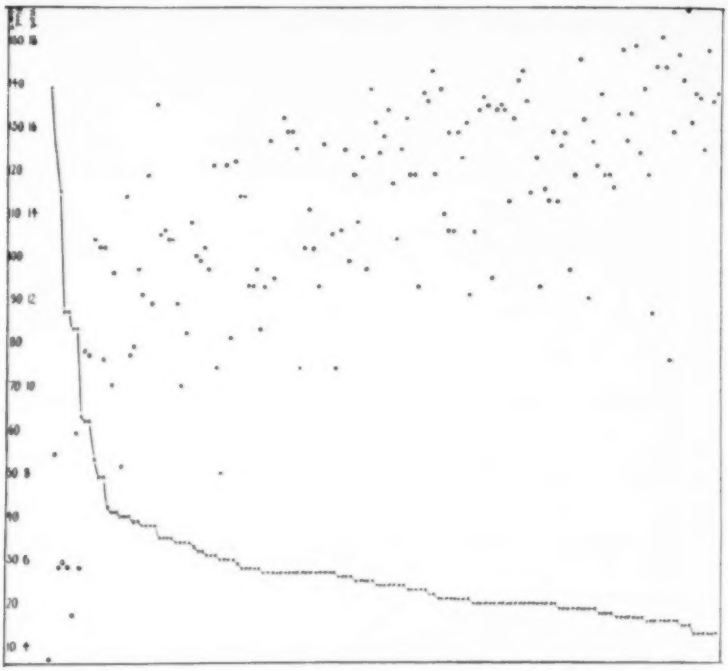

Chart 3.—The relation between the blood urea nitrogen and work done per gram of urea excreted of all observations made.

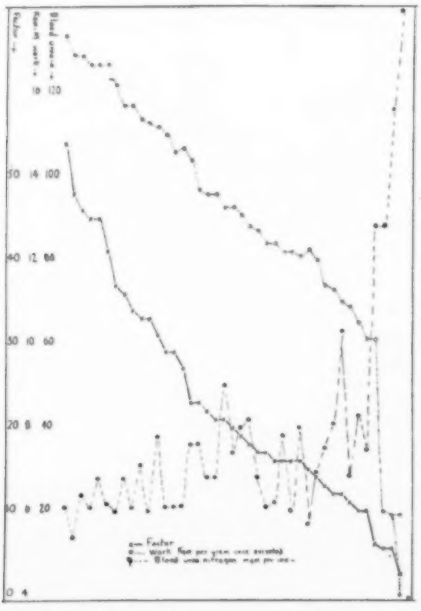

Chart 4.—The relation between the urea concentration factor and the work done per gram of urea excreted.

of urea excreted by the same subjects as shown in Chart 1. Chart 3 shows the relation between the blood urea nitrogen and work done per gram of urea excreted of all observations made. Chart 4 shows the relation between the urea concentration factor and the work done per gram of urea excreted.

TABLE 3.—*Observations Made on Twenty-Nine Patients Showing Albuminuria*

Case	Grams Urea, in 2 Hours	First Blood Urea-Nitrogen	Average Blood Urea-Nitrogen	Per Cent. Concentration Urea, Second Urine	Factor	Total Work, Kilogram-meter	Work, Kilogram-meter per Gm.	Clinical
1	1.31	35	49	1.08	10.2	13.2	10.0	Chronic nephritis
2	3.02	86	93	0.80	4.0	18.1	6.0	Chronic preuremia
	1.90	116	123	1.04	3.9	11.2	5.9	
	1.42	88	96	0.79	3.8	8.3	5.9	
3	2.57	21	25.5	2.94	53.9	44.7	17.4	Orthostatic albuminuria
4	1.85	35	41	1.16	13.2	20.9	11.3	Pyelonephritis
	2.24	21	25	0.92	17.1	27.7	12.4	
	2.53	28	32	1.44	21.0	33.6	13.3	
	4.20	21	24.5	2.38	45.4	70.1	16.7	
5	1.08	28	30	0.72	11.2	11.3	10.5	Vesical calculus
6	2.24	22	27.5	2.42	41.1	36.2	16.2	Chronic nephritis
7	2.12	36	40	1.99	23.2	29.0	13.7	Prostatic enlargement
8	2.78	41	48.5	1.28	12.3	30.5	11.0	Pyelonephritis
9	1.68	63	73.5	1.92	12.2	18.3	10.9	Prostatic pyelonephritis
	2.23	36	46.5	2.25	22.6	30.3	13.6	
	1.79	34	38	1.62	19.9	23.4	13.1	
10	2.73	29	39	1.14	13.6	31.1	11.4	Prostatic enlargement
	2.05	38	45	1.58	16.4	25.0	12.2	
11	1.66	28	35	1.68	22.4	22.5	13.6	Nephroptosis
	2.69	14	17.5	1.80	48.1	43.9	16.9	
12	1.96	28	31.5	1.17	17.3	23.9	12.4	Cystitis
13	1.40	20	24.5	0.85	16.2	16.9	12.1	Tuberculous kidney
	2.30	40	43	1.53	18.6	28.2	12.8	
	3.18	20	28	1.94	32.6	48.3	15.2	
14	3.15	50	53	2.40	21.1	41.8	13.3	Gonorrhea
15	1.01	21	25	1.53	28.6	14.7	14.6	Nephrolithiasis
16	1.57	17	18.5	0.60	15.1	18.5	11.8	Chronic nephritis
17	2.74	28	34	2.64	36.3	43.0	15.7	Chronic myocarditis
18	2.93	21	24.5	1.80	34.3	45.1	15.4	Pyelonephritis
19	0.93	140	144	0.81	2.5	3.6	3.9	Arteriosclerosis
20	3.31	20	28	1.94	32.6	48.3	15.2	Ureteral stone
21	3.77	28	31	3.02	45.5	62.9	16.7	Chronic nephritis
22	4.15	38	36	2.40	31.1	62.2	15.0	Hematuria; tumor ?
23	3.96	20	24.5	1.97	37.5	62.5	15.8	
24	3.80	17	27.5	1.80	30.6	57.0	15.0	Tuberculous epididymo-orchitis
25	1.65	24	28	2.76	46.0	27.5	16.7	Cardiorenal
26	3.01	22	31	1.10	16.5	36.7	12.2	Chronic nephritis
27	3.00	21	28	1.74	29.0	44.1	14.7	Myxedema
28	3.85	42	49.5	1.94	18.3	48.8	12.7	Chronic nephritis
29	1.38	43	50	1.08	10.0	13.9	10.1	Chronic nephritis

COMMENT

Charts 1 and 2 demonstrate that the total work done during a known period cannot be taken as an index of renal efficiency. This is influenced by the rate of absorption of the urea from the alimentary tract. The work done per gram of urea excreted does, however, indicate efficiency and varies, roughly, inversely as the concentration of urea in the blood. From the previous considerations of the factors governing the retention of urea in the blood no strict relation is expected. The factor of absorption of urea is demonstrated by the data in Table 4. The data were obtained from a normal individual, a laboratory worker, by giving him each morning on successive days 15 gm. of urea. The

total grams of urea excreted in two hours and the concentration of urea in the blood at the end of this period were noted. For these calculations it is assumed that urea is evenly distributed throughout the body fluids and that 1 kg. of body substance contains approximately 700 c.c. of water. In this subject, therefore, each gram of urea absorbed from the alimentary tract should, if not excreted, increase the concentration of the blood urea nitrogen by 1.5 mg. per hundred cubic centimeters. It will be noted that according to the above assumptions as much as 5 gm. failed to be absorbed during one period.

TABLE 4.—*Rate of Absorption of Urea*

	Normal Subject. Weight of Body Fluids, 65 Kg.				
			Blood Urea-Nitrogen		
Day	Urea Ingested, Gm.	Urea Excreted, in 2 Hours	Calculated	Actual	Urea Not Absorbed, Gm.
1	15	5.12	15.0	14	0.65
2	15	4.11	16.7	14	1.70
3	15	4.77	15.7	7	5.60
4	15	4.71	15.8	8	5.00
5	15	5.16	15.1	11	2.60
6	15	4.67	15.8	10	3.70

When performed under the uniform set of conditions (post absorptive state, limited water intake, etc.) the normal amount of work done is regarded as 17 kilogram-meters per gram of urea excreted. That this value may be made to vary when the test is not performed under the conditions described is quite obvious. The data in Table 5 show the

TABLE 5.—*Effect of Water Intake on Work Done (Normal Subject)*

Day	Water Intake, C.c.	Urine Urea Excreted in 2 Hours	Blood Urea-Nitrogen, Average	Urine Urea Concentration Second Hour	Factor	Work, Kilogram-meter per Gm. Urea Excreted
1	150	5.12	28.0	3.12	52.0	17.3
2	250	4.11	28.0	2.98	49.7	17.1
3	500	4.77	24.5	2.16	41.1	16.2
4	1,000	4.71	25.0	0.78	14.5	11.7
5	1,500	5.16	26.5	0.49	8.6	9.4
6	2,000	4.67	26.0	0.42	7.5	8.8

effects of varying the amount of water intake. The test was performed under the standard conditions described except that each day the quantity of water taken was varied. On successive days the subject, a normal person, was given 15 gm. of urea dissolved in 150, 250, 500, 1,000, 1,500 and 2,000 c.c. of water, respectively. It will be noted that varying the quantity of water did not effect the rate of urea excretion. This has previously been demonstrated.[5] The effect was to lower the value of the urea concentration factor, and thus lower the amount of work done. It appears that this observation may have some therapeutic

5. Addis, T., and Drury, D. R.: The Rate of Urea Excretion, J. Biol. Chem. **55**:639 (April) 1923.

significance. By increasing the water intake and making the kidneys excrete a less concentrated urine the same amount of urea was excreted with less work. It is here assumed that the excretion of water does not, as compared with the excretion of urea, require that much work must be done by the kidneys. This was demonstrated by the work of Barcroft and Straub.

For practical purposes, to obtain the work done per gram of urea excreted, it will be noted from the formula that the specimen of urine need not be quantitatively collected since the work done per gram of urea excreted may be calculated from the logarithm of the factor. Thus $10.1 \times \text{Log}_{10}$ factor = Kilogram-meters work per gram urea excreted.

CASES OF MARKED HYPERTENSION, ADEQUATE RENAL FUNCTION AND NEURORETINITIS

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During the last three years a number of patients with hypertension and neuroretinitis have been referred from the Mayo Clinic to the medical service at the hospital with the diagnosis of chronic, diffuse, glomerular nephritis. In several of these, on further study, we found that the history and clinical findings differed from those usually found in cases of chronic nephritis, and also that the renal function was surprisingly good. The case reported here (Case 11) is an example of a group which seems to form a definite clinical type.

REPORT OF CASE

CASE 11.—A man, aged 45, sought medical advice at the Mayo Clinic because of severe headaches, general weakness, nervousness and loss of weight. Five years before, during treatment for dermatitis, his physician had noted increased blood pressure and albumin in the urine. Until one year before admission he had continued in good health, and had carried on his business successfully. At that time he began to have frequent occipital headaches which gradually increased in severity. Six months before, he had noticed that he was becoming nervous; he worried over minor details and could not sleep. From then until the physical examination he had lost 40 pounds (18 kg.) in weight. During the last month his vision had occasionally been slightly blurred.

The patient seemed to be seriously ill, but aside from his blood pressure reading, 250 systolic and 190 diastolic, nothing alarming could be demonstrated. His heart was moderately enlarged, the peripheral vessels were definitely thickened, but there was no gross evidence of cardiac incompetency, such as pulmonary congestion or dependent edema. The mucous membranes were normal in appearance. Vision was impaired in one eye and normal in the other. The ophthalmoscope revealed severe neuroretinitis. Examination of the urine revealed the presence of a moderate amount of albumin and a few hyaline casts. The patient was kept under observation in the hospital for two weeks. There was no anemia, and slight, if any, disturbance of cardiac or renal function; nevertheless the nervousness, headache and insomnia continued and the retinitis did not improve. It seemed logical to believe that the disease was progressive and would soon lead to more serious symptoms, and this was confirmed by the patient's death five weeks after his dismissal from the hospital. Exact details of the last weeks of his illness were not obtainable, but a cerebral accident was probably the cause of death. The detailed findings in this and thirteen similar cases seem to differentiate them from chronic, diffuse, glomerular nephritis, and to justify their discussion as a group.

SYMPTOMS AND PHYSICAL FINDINGS

The patients' ages varied from 24 to 49 years, the average being 39. The onset of symptoms before examination at the clinic varied from a few months to three years. Severe headache and other subjective or

objective nervous symptoms were at some time, or always present. There were evidences of serious cerebral involvement in eight of the fourteen cases. In four, there was hemiplegia or monoplegia. In four, convulsions occurred; in three of these, tumor of the cerebrum was suspected and considered, in one of which a subtemporal decompression was performed elsewhere with negative findings. Subjective disturbances of vision occurred in five cases, the symptoms varying from slight blurring sensations to almost complete blindness. In certain cases, the absence of visual disturbances with considerable retinal involvement, was striking. Loss of weight and strength occurred in half of the cases, the most marked loss of weight (75 pounds, 34 kg.) occurring in the short period of six months. Symptoms of cardiac insufficiency, such as dyspnea and dependent edema, were not the rule, and when present, were minor in degree. Urinary symptoms were rarely complained of, and consisted of slight and moderate nocturia in half the cases. The urine had been examined previously in six cases, and albumin found in each, the history dating back in one case for eight years.

Although the patients were able to be up and about, they were all sent to the hospital for observation and for study periods, varying from one to seven weeks. Several were seen first in the Section on Ophthalmology because of eye symptoms, and when the retinal changes were found, a general examination was advised. A thorough physical examination was made, particular attention being given to the cardiovascular system. Clinical evidences of anemia were absent. Thickening of the brachial artery could always be demonstrated, the degree of change varying from a palpable thickening to tortuosity and beading. Examination of the heart by palpation and percussion revealed enlargement in twelve cases. The point of maximal impulse was outside the left mammary line. In some cases it could be felt in the axilla. In two cases, no cardiac enlargement was noted. The second heart sound was accentuated over the aortic area in thirteen of the cases. In the one case in which the second pulmonic sound was accentuated, there was an apical, systolic murmur with cardiac enlargement, so that the absence of a clicking, aortic second sound might well be due to a relative mitral insufficiency. Apical systolic murmurs were present in half the cases, and in five of these there was an associated aortic systolic murmur. No serious disturbance of the cardiac rhythm was observed. These cardiac findings are similar to those noted by Shaw [1] in his study of hyperpiesia.

At the time of examination the blood pressure was high. The maximal reading varied from 210 to 280 systolic and 140 to 190 diastolic.

1. Shaw, H. B.: Hyperpiesia and Hyperpiesis, London, Frowde, Hodder and Stoughton, 1922, p. 191.

TABLE 1.—*Clinical Findings*

Case, Sex* and Age	Date	History of Present Illness	Physical Examination †	Blood Pressure				Retinal Changes	Electrocardiogram	Appearance of Nail Fold Capillaries	Result
				On Admission		At Dismissal					
				Systolic	Diastolic	Systolic	Diastolic				
1 ♀ 24	4/27/22	Tuberculous infection, right foot for twelve years; hypertension for seven years; headache and blurring vision for two months	Heart enlarged 1; aortic and apical systolic murmur; second aortic accentuated; peripheral sclerosis 2	280	190	210	140	Moderate arteriosclerosis; well developed neuroretinitis	Normal	Moderate morphologic and functional changes	Death, 3/26/23
2 ♀ 45	8/26/21	Right hemiplegia six months, and vertigo, weakness, dyspnea and dimness of vision two months before; hypertension for six months; lost 75 pounds (34 kg.) in last six months	Heart enlarged 1; faint apical systolic murmur; second aortic accentuated; peripheral sclerosis 2	250	140	...	...	Moderate arteriosclerosis; well developed neuroretinitis	.....	.....	Death, 8/31/21; cerebral hemorrhage; necropsy
3 ♂ 40	9/23/21	Periodic headaches for five years, severe for three; hypertension for one year; occasional edema of ankles at night	Heart enlarged 2; faint apical systolic murmur; second aortic accentuated; peripheral sclerosis 1 to 2	235	150	170	110	Moderate arteriosclerosis; early neuroretinitis	Normal	Only slight changes	Death, January, 1923
4 ♂ 25	10/24/21	Headache, loss of vision and loss of weight for twenty months; Jacksonian and grand mal attacks of epilepsy for fourteen months; hypertension for eighteen months; tumor cerebri ?; subtemporal decompression 8/21/20	Heart not enlarged; systolic murmur over apex and aortic area; second aortic accentuated; peripheral sclerosis 1; bulging mass right temporal region	240	165	190	130	Marked arteriosclerosis; secondary optic atrophy	Inverted T-wave in Lead 1	No striking abnormality	Death, 12/31/21
5 ♂ 40	12/21/20	Nocturia one year; failing vision for seven months; progressive diminishing vision, two months; general convulsion while in hospital; tumor cerebri ?	Heart enlarged 1; systolic murmur at apex and pulmonic area; second pulmonic accentuated; peripheral sclerosis 2 to 3	240	160	225	140	Moderate arteriosclerosis; well developed neuroretinitis	.....	.....	Death, 1/29/21
6 ♂ 31	4/18/21	Headache and slight polyuria for from two to three years; impaired vision for six months; epileptiform convulsions and hypertension, six weeks; tumor cerebri ?	Heart not enlarged; second aortic accentuated; peripheral sclerosis 1	260	160	225	155	Marked arteriosclerosis; well developed neuroretinitis	.....	.....	Death, 7/8/21

7 ♂ 38	7/13/23	Headache, one year; loss of strength and weight (65 pounds, 29.5 kg.), slight dyspnea and edema; four months before, blood pressure 250	Heart enlarged 2 to 3; systolic murmur at apex and aortic area; second aortic accentuated; peripheral sclerosis 2 to 3	255	155	230	140	Mild arteriosclerosis; well developed neuroretinitis	Inverted T-wave in Leads 1 and 2	Small contracted type	Death, 10/15/23
8 ♂ 45	3/15/23	Nocturnal occipital headache for two years; lost 20 pounds (9 kg.) in three months; hypertension for five weeks	Heart enlarged 1; second aortic accentuated; peripheral sclerosis 1	225	145	175	95	Marked arteriosclerosis; mild neuroretinitis	Normal	.....	Condition satisfactory, 1/29/24
9 ♂ 40	11/ 6/23	Nocturnal headache for two years, severe with slight dyspnea for four months; hypertension for two years	Heart enlarged 1; second aortic accentuated; peripheral sclerosis 2	200	100	210	150	Moderate arteriosclerosis; well developed neuroretinitis	.....	.....	Condition satisfactory, 2/23/24
10 ♂ 45	11/ 8/23	Severe nocturnal headache and hypertension for two years; lost 40 pounds (18.1 kg.) in one year	Heart enlarged 1; second aortic accentuated; peripheral sclerosis 2	200	120	210	150	Moderate arteriosclerosis; early neuroretinitis	.....	.....	Death, 2/8/24
11 ♂ 45	11/ 3/23	Occipital headache for one year; hypertension for five years; insomnia, loss of weight and nervousness for seven months	Heart enlarged 1; second aortic markedly accentuated; peripheral sclerosis 2	250	190	190	145	Moderate arteriosclerosis; well developed neuroretinitis	Normal	Slight narrowing and tortuosity	Death, 12/25/23
12 ♂ 45	2/ 8/23	Headache for three years, severe for one year; loss of weight, 45 pounds (20.4 kg.); hypertension for three months	Heart enlarged 1; second aortic accentuated; peripheral sclerosis 2	250	175	195	115	Marked arteriosclerosis; early neuroretinitis	Inverted T-wave in Leads 1 and 2	.....	Death, 7/28/23
13 ♂ 47	11/24/22 11/15/23	Albumin and casts in urine for eight years; frontal headaches and occasional nocturia for six months; hypertension for one year; right hemiplegia two months before second admission	Heart enlarged 1; second aortic accentuated; peripheral sclerosis 1 to 2	220 180	140 130	180 180	120 120	Mild arteriosclerosis; mild neuroretinitis	Normal second admission	Nothing definitely abnormal	Condition satisfactory one year after first admission
14 ♂ 49	9/26/23	Migraine for years; severe headache, slight hemiplegia and hypertension for two years; severe headache, slight dyspnea and edema for two months	Heart enlarged 2; systolic murmur at apex and aortic area; second aortic accentuated; peripheral sclerosis 3	215	140	210	150	Evidences of hypertension; early neuroretinitis	Inverted T-wave in Leads 1 and 2	....	Death, 10/27/23

* In this column, ♀ indicates female, ♂ male.
† Grade 1 to 4 signifies variation from slight but definite change to most marked.

Thirteen of the patients had known that they had hypertension. After several days of hospital treatment there was a fall in the pressure. The treatment consisted of periods of rest in bed, sedatives for insomnia and restlessness, hot baths and the periodic use of sodium nitrite. The blood pressure readings on dismissal from the hospital varied from 140 to 215 systolic, 80 to 140 diastolic (Table 1). Observations on the effect of repeated doses of sodium nitrite were made in seven cases. A temporary fall in blood pressure occurred, the systolic fall being more marked than the diastolic. The extent of the fall was considered an index of vasomotor response. The temporary effect of a hot bath on the hypertension was also noted. The fall in blood pressure was not usually so marked as after nitrite had been given (Table 2).

TABLE 2.—*Effect of Sodium Nitrite and Hot Bath on Blood Pressure*

		Blood Pressure							
		Sodium Nitrite, 0.03 Gm. by Mouth, Hourly for Six Consecutive Doses				Hot Bath, Water at Temperature of From 95 to 110 F. for From 10 to 20 Minutes			
		Before		1 Hour After Last Dose		Before		1 Hour After Bath	
Case	Date	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
7	7/14/23	230	120	200*	110*	...	...	...	...
	7/23/23	...	...	...	...	230	130	220	130
8	3/15/23	210	120	140	100	...	...	...	...
9	11/ 4/23	230†	160	170	120	...	...	...	...
	11/ 5/23	...	...	...	...	220	140	190	120
	11/21/23	...	...	...	...	210	140	215	135
10	11/18/23	...	...	...	...	200	145	190	130
11	11/ 4/23	210†	150	180	125	...	...	...	...
	11/ 9/23	...	...	...	...	215	140	210	150
	11/13/23	...	...	...	...	220	150	205	150
12	2/ 9/23	210	100	150	90	...	...	...	...
13	11/15/23	175	110	150	70	...	...	...	...
	11/18/23	...	...	...	...	170	100	160	105
14	9/29/23	220	140	180	110	...	...	...	...
	9/30/23	...	...	...	...	230	150	230	150
	10/ 1/23	...	...	...	...	230	150	210	130
	10/ 4/23	220	140	190	125	...	...	...	...

* Taken immediately following sixth dose of sodium nitrite.
† 0.03 gm. sodium nitrite given half-hourly for six consecutive doses.

In six cases, the nail fold capillaries were examined. In one case, they were definitely contracted, while in the others, no abnormalities, or only minor functional disturbances were observed.

In nine cases, electrocardiographic tracings were taken. Sinus rhythm was present in all, thus confirming the clinical observation that abnormal rhythms were not observed. In five cases the tracing did not reveal abnormalities; in four there were different degrees of T-wave negativity.

Retinal Changes.—In all of the cases, ophthalmoscopic examination revealed neuroretinitis associated with retinal vascular changes (Table 3). In Case 14, there was no definite retinal arteriosclerosis,

TABLE 3.—*Retinal Findings*

Case	Date	Hyperemia of Disks*	Edema of Disks, Diopters		Edema of Peripapillary Retina	Snow-bank Exudates	Cotton-wool Exudates	Edema absorbing Exudates	Macular Star	Retinal Hemorrhages	Peripheral Pigment Deposits	Retinal Detachment	Reduction in Caliber of Arteries	Irregularity in Caliber of Arteries	Exaggerated Arterial Reflex	Relative Engorgement of Veins	Arteriovenous Compression	Perivasculitis	Choroidal sclerosis	Postneuritic Optic Atrophy	Vision		Course Under Observation
			Right	Left																	Right	Left	
1	4/22/22	+		2	+	—	+	+	+	+	—	—	+	+	+	+	+	—	—	—	....	....	Slight improvement
2	8/26/21	..	3	1	..	—	+	..	Partial	+	—	—	+	+	+	+	+	—	—	—	....	....	Slight improvement
3	9/23/21	..		+	+	—	+	+	—	+	—	—	+	+	+	+	+	—	—	—	....	....	
4	10/24/21	—	Previous 6	5	—	—	—	—	—	+	+	—	+	+	..	+	+	+	+	+	Moving objects		
5	12/31/20	..	6	4	+	+	+	+	—	+	+	—	+	+	+	+	+	+	—	—	Counts fingers		Progression
6	4/18/21	..	1-2		+	+	+	+	+	+	+	1	+	+	+	+	+	—	—	..	....	....	
7	7/13/23	+	1-2	2	+	—	+	+	—	+	+	—	+	—	+	+	+	+	+	..	....	....	No change
8	3/15/23	..		+	+	—	+	—	—	+	—	—	+	+	+	+	+	+	—	..	6/6	6/6	Improvement
9	11/ 6/23	—		1	+	—	+	+	—	+	—	—	+	+	+	+	+	+	—	..	....	....	No change
10	7/11/23	+		+	+	—	—	—	—	—	—	—	+	+	—	—	—	—	—	..	6/6	6/6	Progression
	11/ 8/23	+	1	1	+	—	+	+	—	+	—	—	+	+	—	—	—	—	—	—	6/6	6/6	
11	11/ 3/23	+	1	2	+	—	+	—	Partial left	+	+	—	+	+	+	+	+	+	—	—	6/60	6/7	Slight improvement
12	2/ 8/23	..		+	+	—	+	—	—	+	—	—	+	+	+	+	+	—	—	—	6/6	6/6	
13	11/24/22	..		+	+	—	+	—	—	+	—	—	+	+	+	+	+	—	—	—	6/10	6/6	Improvement
14	9/26/23	+		1	+	—	+	—	—	+	—	—	+	—	+	+	+	—	—	—	6/10	6/12	Slight improvement

* + signifies present, — not present.

but there was exaggeration of the reflex stripe of the arteries, engorgement of the veins, and arteriovenous compression. In the other cases, there were varying degrees of arteriosclerosis of the hypertension type characterized by reduction and irregularity in caliber of the arteries. In Cases 4, 6, 9 and 11 perivasculitis was present, probably secondary to inflammation of the surrounding retina. In Cases 8 and 13, the neuroretinitis was of mild type, and was characterized by edema of the disc and retina, with scattered cotton wool exudates and hemorrhages, which tended to become fewer during the stay of the patients in the hospital.

In the other twelve patients, a severe and characteristic type of neuroretinitis was found. Cases 3, 10, 12 and 14 demonstrated what we regarded as an early stage of this retinitis. There were hyperemia and edema of the optic discs with swelling measurable from 1 to 2 diopters, edema of the peripapillary retina extending for varying distances toward the periphery, flame shaped and deep retinal hemorrhages, and cotton-wool exudates, or localized areas of increased density in the general edema. In Cases 1, 2, 5, 6, 7, 9 and 11, there was well developed neuroretinitis, which probably had been present for several weeks. The retinal picture was that of "albuminuric retinitis." The swelling of the discs varied from 1 to 6 diopters. Besides the edema of the retina, cotton-wool exudates and hemorrhages, there were scattered through the retina, especially between the disc and macula, bright white punctate exudates of the "absorbing-edema type." Peripherally, in regions from which the edema had subsided, there were small clumps of displaced pigment, often with a faint surrounding halo of choroidal atrophy. In Cases 5 and 6, the edema of the peripapillary retina was sufficiently dense to be described as "snow-bank." Partial or complete macular stars were present in Cases 1, 6 and 11. Localized retinal detachments occurred only in Case 5. In Case 4 there was postneuritic atrophy of the optic nerve, marked postinflammatory sclerosis of the retinal vessels, and atrophic and pigmentary changes in the retina and choroid. These, we believed to be the end-results of a severe neuroretinitis of the type seen in the other cases, and reports of previous fundus examination by other oculists confirmed our opinion.

Laboratory Findings.—The erythrocyte count and hemoglobin determinations confirmed the clinical observation that definite anemia was practically never present. In Case 5, the erythrocytes numbered 4,600,000 at one examination; the hemoglobin was 60 per cent., Dare; later it rose to 65 per cent. The erythrocytes occasionally numbered 4,000,000 on the patient's admission to the hospital, but when checked later, practically always rose. The leukocytes were determined in twelve cases. In ten of these, the count varied from 5,000 to 11,000; in one case it was 13,000. This patient developed a fatal cerebral hemorrhage

TABLE 4.—*Laboratory Findings*

		Blood								Urine								
										Specific Gravity					Chlorid Test, % Concentration§			
Case	Date	Erythrocytes, Millions	Hemoglobin, per Cent. (Dare)	Leukocytes	Wassermann Reaction	Urea, Mg. in Each 100 C.c.	Creatinin, Mg. in Each 100 C.c.	Uric Acid, Mg. in Each 100 C.c. (Folin and Wu)	Plasma Chlorids, Mg. in Each 100 C.c.	Variation	With Concentration Test	With Water Test	Albumin‡	Casts‡	Phenolsulphonephthalein Excretion, 2 Hours, per Cent.	Before Injection	After Injection	Sodium Benzoate Excretion, 3 Hours
1	4/27/22	4.60	76	7,000	—	18	...	...	...	1.009-1.02†	.....	.....	1-3	0	45	...	...	.....
	5/17/22	.....	111*	.....	..	15	...	...	...	.....	.....	.....	...	...	..	...	...	.....
2	8/26/21	5.10	82	13,000	—	34	1.9	...	...	1.006-1.026	.....	1.006	1	Occasional	..	...	...	.....
3	9/23/21	.....	76	10,700	—	29	1.6	3.1	...	1.001-1.027	1.027	1.001	1-3	1-3	60	...	...	.....
	10/27/21	.....	...	.....	..	41	1.5	4.0	...	.....	.....	.....	...	...	..	...	...	.....
	10/31/21	4.60	76	8,400	..	51	1.6	3.8	...	.....	.....	.....	...	...	50	...	...	.....
	11/14/21	.....	...	.....	..	21	1.6	2.8	...	.....	.....	.....	...	...	..	...	...	.....
	2/10/22	4.50	75	8,400	..	38	...	3.9	...	1.004-1.028	1.028	1.004	...	...	45	...	...	.....
4	10/24/21	4.70	78	6,400	—	27	1.4	3.6	...	1.006-1.034	1.034	.....	1	Occasional	65	..	...	.....
5	12/31/20	4.60	60	20,000	—	34	1.6	1.9	...	1.004-1.016	.....	.....	1-3	1-3	40	..	...	.....
	1/11/21	4.25	65	12,000	..	42	1.6	2.9	...	.....	.....	.....	...	...	..	...	...	.....
6	4/21/21	4.46	74	8,200	—	46	1.5	3.4	500	1.003-1.030	1.027	1.003	1-2	1-2	70	...	...	.....
	4/29/21	.....	...	.....	..	35	1.5	2.7	600	.....	.....	.....	...	...	..	...	...	.....
7	7/13/21	.....	114*	.....	..	29	1.8	4.0†	...	1.001-1.036	1.030	.....	1-2	...	40	...	...	.....
8	3/12/23	4.00	76	6,700	..	22	...	...	...	.....	.....	.....	...	...	..	...	...	.....
	3/15/23	4.70	78-100*	5,000	—	32	1.7	3.7†	...	1.002-1.027	1.027	1.002	0-1	1	65	0.8	1.4	87% normal
9	11/ 6/23	.....	127*	.....	..	37	2.3	5.1†	...	1.003-1.026	.....	1.003	1-2	1-3	..	1.3	3.2	.....
	11/14/23	5.35	92	8,800	—	41	2.4	5.7†	665	.....	.....	.....	...	...	45	...	...	.....
10	11/ 8/23	4.10	75	7,200	—	32	2.2	4.8†	615	1.007-1.020	1.020	.....	1-2	1	30	0.3	0.2	.....
	11/15/23	.....	...	.....	..	..	...	...	...	.....	.....	.....	...	...	30	...	...	.....
11	11/ 3/23	4.60	75	9,000	—	34	...	...	...	.....	.....	.....	...	...	..	...	...	.....
	11/ 6/23	4.50	81	.....	..	31	2.0	4.4†	575	1.001-1.020	1.020	1.001	1-2	1	45	0.7	1.5	.....
12	2/ 8/23	4.90	79-108*	4,700	—	55	2.7	4.5†	595	1.009-1.015	1.014	.....	1-2	1	35	0.3	0.1	.....
	2/19/23	.....	95*	.....	..	25	2.4	3.3†	...	.....	.....	.....	...	...	..	...	...	.....
13	11/24/22	4.60	76-119*	6,000	—	32	...	3.2†	...	1.001-1.031	1.028	1.001	0-1	0-1	55	..	...	.....
	11/15/23	.....	118*	.....	..	22	1.7	2.4†	570	1.002-1.027	1.027	1.002	0-1	0	40	0.7	2.3	.....
14	9/26/23	.....	118*	.....	—	29	2.3	3.6†	...	1.005-1.025	1.025	.....	1-2	1	55	...	...	.....

		Urine	
		Output Water Test, C.c.	
1	4/27/22	.....	
	5/17/22	.....	
2	8/26/21	905	
3	9/23/21	1,145	
	10/27/21	.....	
	10/31/21	.....	
	11/14/21	.....	
	2/10/22	1,540	
4	10/24/21	.....	
5	12/31/20	.....	
	1/11/21	.....	
6	4/21/21	1,030	
	4/29/21	.....	
7	7/13/21	.....	
8	3/12/23	.....	
	3/15/23	1,110	
9	11/ 6/23	.....	
	11/14/23	760	
10	11/ 8/23	.....	
	11/15/23	.....	
11	11/ 3/23	.....	
	11/ 6/23	1,030	
12	2/ 8/23	.....	
	2/19/23	.....	
13	11/24/22	1,005	
	11/15/23	1,025	
14	9/26/23	.....	

* Haldane-Palmer carbon monoxid, or Osgood acid hematin methods.
† Folin new method described in J. Biol. Chem **54**: 153, 1922.
‡ Albumin and casts have been graded from 1 to 4. One equals smallest amount or number, 4 the largest.
§ Normal chlorid per cent. concentration, before injection of from 0.8 to 1.9, after injection of from 1.8 to 2.0.

within a few days. In Case 5, the leukocyte count was 20,000. The cause of this temporary leukocytosis was not determined. In thirteen cases, the Wassermann reaction in the blood was negative. In two of these, it was also negative in the spinal fluid. It is of interest that there was no history or physical findings suggestive of syphilitic infection in any of these cases (Table 4).

Urinary Findings.—Albumin, casts, and a few erythrocytes and leukocytes were found at one or more examinations in each case. The amount of albumin varied markedly even in the same case. In three cases, a heavy precipitate was occasionally found. In only four cases was the number of hyaline and granular casts at any time numerous. Cellular casts, actual pyuria or hematuria were not observed.

Normally, the specific gravity of the urine varies between 1.003 and 1.030. In six of the cases in this series the variation was approximately normal. In four, the variation was slightly decreased, although the optimal conditions for concentration and dilution were not obtained. The drinking of a large amount of water was found to aggravate the nervous symptoms of certain of these patients so that the test was sometimes omitted. On the other hand, certain patients found the dry diet unpalatable. Under satisfactory conditions, three patients were unable to excrete a concentrated urine. The maximal specific gravity never rose above 1.020.

Water Excretion.—The water test was satisfactorily carried out in seven cases. In one, Case 2, the specific gravity of the urine failed to fall to 1.003. In four cases, the total urine output was normal or slightly reduced, with the curve of excretion and fall in specific gravity within the normal limits. In two, the urine output was reduced, while in one the curve of excretion was abnormal.

The phenolsulphonephthalein excretion was determined in thirteen cases. In seven, the output, at least on one occasion, was 50 per cent. or higher; in four, from 40 to 45 per cent.; while in two, it was from 30 to 35 per cent. In the latter two cases, total renal function was distinctly impaired. In six cases, 5 gm. of sodium chlorid was injected intravenously, according to the technic instituted by Barrier and Whelan.[2] In four cases, the excretion was normal or slightly reduced, while in two, it was abnormally decreased. The sodium benzoate test of Kingsbury[3] was carried out in a single case (Case 8), and a normal result obtained.

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2. Barrier, C. W., and Whelan, Mary: Personal communication.

3. Kingsbury, F. B., and Swanson, W. W.: The Synthesis and Elimination of Hippuric Acid in Nephritis: A New Renal Function Test, Arch. Int. Med. **28**:220-236 (Aug.) 1921.

CHEMICAL STUDIES OF THE BLOOD

The urea content of whole blood was normal in eight cases, ranging from 15 to 34 mg. for each 100 c.c. In three cases the values bordered on the abnormal, varying from 35 to 42 mg. There was a distinct increase above the normal in the three remaining cases, the amount varying from 46 to 55 mg. The patient, Case 3, was under observation in the hospital for a period of seven weeks, and for one of two weeks. During the first period, the blood urea was determined at weekly intervals; in five instances the amount was below 31 mg.; while in two, it was 41 and 51 mg. At the time of the two latter determinations, there were no other evidences of definite renal insufficiency. These findings indicate that fluctuations in the urea content of the blood may occur in this type of renal injury, but even under such severe testing, the amount does not reach the level so commonly observed in cases of chronic, diffuse, glomerular nephritis. In only one of three cases (Case 12) in which the values were from 46 to 55 mg. was the renal function distinctly impaired.

The creatinin content of whole blood was determined in thirteen cases, and in only four was it above 2.0 mg. for each 100 c.c. The increased values varied from 2.2 to 2.7 mg. and in three, including Case 12, there was an associated increased blood urea.

Estimations of the uric acid concentration in the whole blood were made in twelve cases. The findings in five were within normal limits; in the seven remaining cases, the abnormal increase was never striking in amount and not necessarily associated with measurable impairment of renal function.

The chlorid content of the plasma was determined in six cases. In only one, Case 9, was the amount abnormally increased, amounting to 665 mg. for each 100 c.c. In this case, there was no visible edema or inability to excrete sodium chlorid, although extra water was not satisfactorily eliminated.

PATHOLOGIC FINDINGS

Only one patient of this series (Case 2) died while under observation. Cerebral symptoms associated with left-sided weakness developed suddenly, and in a few hours the patient lapsed into deep coma and died forty-eight hours later.

Necropsy Findings.—Bilateral cerebral hemorrhage, marked cardiac hypertrophy, moderate generalized arteriosclerosis, arteriosclerotic change of the kidneys and terminal bronchopneumonia were noted. On sectioning the brain, both ventricles were found filled with blood, the amount of blood being greater in the left. The heart weighed 400 gm. and there was marked hypertrophy of the left ventricle. Scattered throughout the coronaries were small yellowish areas of

thickening, but the lumen was patent throughout. The kidneys weighed 135 gm. each. The capsule was adherent, and when stripped revealed a fine granular surface. On section, the cut surfaces showed some pale areas and in the pelves of both kidneys there were discrete punctate areas of hemorrhage.

There were numerous focal areas of increase of the interstitial connective tissue in the cortex. In the intervening portions, the glomeruli were often considerably increased in size, some of them fully twice the size of a normal glomerulus. The glomeruli showed occasional thickening of the capsules and lobulation and partial hyalinization of the tufts with an irregularity in the form of the capsule itself. Occasionally a glomerulus was completely obliterated.

The arteries showed distinct thickening of the intima and the inner portion of the media, with hyalinization. Calcareous particles were seen in the medullary portions adjacent to the tubules. The tubular epithelium was in fairly good condition. The lumina of the tubules were occasionally dilated and there were a few cysts. An occasional hyaline cast was seen in the limbs of Henle's loops. A microscopic diagnosis of moderate renal arteriosclerosis was made.

Eleven other patients are known to have died since they were observed in the clinic, but no accurate data on the immediate cause could be obtained.

COMMENT

Volhard and Fahr [4] have used the term "malignant hypertension" to indicate those cases of vascular sclerosis which later develop definite renal insufficiency. On the other hand, we have limited the term to those cases of severe, diffuse, vascular disease which do not show distinct renal insufficiency. The term "malignant" is applicable to these cases because of the frequent loss of weight, cerebral symptoms and accidents, continued high blood pressure, severe neuroretinitis and the serious prognosis. The age incidence, history, clinical and laboratory findings are similar to those in the severe cases of so-called essential hypertension or hyperpiesia described by Allbutt.[5] The persistent hypertension, cardiac enlargement, peripheral sclerosis, retinal changes, absence of anemia, and only moderate or no reduction in renal function seem to constitute a distinct clinical entity.

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4. Volhard, F., and Fahr, K. T.: Die brightsche Nierenkrankheit, Klinik, Pathologie, und Atlas, Berlin, Julius Springer, 1914, p. 300.

5. Allbutt, C.: Senile Plethora, or High Arterial Pressure in Elderly Persons, Tr. Hunterian Soc., 1895-1896, pp. 38-57 (quoted in Diseases of the Arteries, Including Angina Pectoris, New York, The Macmillan Company, **1**:10, 1915); An Address on Arteriosclerosis and the Kidneys, Brit. M. J. **1**:853, 922-936, 1911.

Volhard and Fahr,[4] Shaw,[1] and Ellis and Marrack[6] have pointed out several features differentiating these cases from chronic glomerular nephritis, namely, higher blood pressure, absence of anemia, adequate renal function, and absence of extensive diffuse lesions in the kidneys at necropsy. Taking this series of cases as a whole, disturbances of renal function, when present, were never severe. In certain cases there was no abnormality except a trace of albumin and a few casts, in others diminished excretion of water, chlorids, and phenolsulphonephthalein were noted, but not enough to derange general metabolism, or produce abnormal symptoms. Analyses of the blood in the majority of cases revealed no evidence of nitrogen retention. When it was present, the increase above normal was so slight that it could not be termed azotemia. We believe that, besides the foregoing differences, the severe hemorrhagic and exudative neuroretinitis, while "albuminuric" in type, has certain distinctive features. Chief among these are the presence of definite retinal arteriosclerosis of the hypertension type and the absence of anemia. Retinal edema is usually not so extensive and less often assumes the "snow-bank" type, and macular stars are less common than in the nephritic cases. Behan[7] has mentioned the occurrence of neuroretinitis in patients with high blood pressure without renal insufficiency. In a series of papers, Benedict[8] has called attention to the effect of hypertension on the retinal vessels, and to the influence of vascular changes and toxemia in the production of retinitis in cardiovascular renal disease. He cited several cases in which the renal function was good at the time of examination. In some of these he suggested the possibility of a transitory preceding or subsequent renal insufficiency.

The diagnosis of cerebral tumor was seriously considered in three cases. That cerebral tumor and malignant hypertension may have been present in the same patient is quite possible, but as necropsies were not performed, the diagnosis of tumor could not be made. In Case 4, an exploratory craniotomy failed to reveal a tumor. On the other hand, Hench[9] has found that hypertension rarely occurs in undoubted

6. Ellis, A. W. M., and Marrack, J. R.: An Investigation of Renal Function in Patients with Retinitis and High Blood Pressure, Lancet **1**:891-893 (May 5) 1923.

7. Behan, J. L.: The Fundus Changes in Nephritis, J. A. M. A. **78**:1691-1694 (June 3) 1922.

8. Benedict, W. L.: Retinitis Associated with Disease of the Cardiovascular System, New York M. J. **117**:741-745 (June 20) 1923.

9. Dr. P. S. Hench investigated the blood pressure findings in a group of forty-four patients with brain tumors in the clinic. The tumor was actually demonstrated at operation or necropsy or at both examinations. The age incidence was from 20 to 51 years. Only two patients had a systolic blood pressure of over 150. In one, a woman, aged 51, the blood pressure on admission was 186 systolic and 120 diastolic, and nine days later was 150 systolic and 90 diastolic. There was evidence of sclerosis in the retinal arteries. The second case was a man, aged 43. The blood pressure was 152 systolic and 100 diastolic with no evidence of arteriosclerosis.

cases of brain tumor. Thus the high blood pressure and certain differential points in the retinal findings, particularly the presence of arteriosclerosis and the distribution of the edema, lead us to believe that the symptoms suggesting cerebral tumor are secondary to the hypertensive vascular condition.

The prognosis in twelve of these cases was extremely serious. Eleven patients died within from a week to fifteen months of their initial examination in the clinic. The remaining patient left the hospital November, 1923, and he is still able to do his work though his headaches are persistent and severe.

In Cases 8 and 13 the hypertension on admission to the hospital was not so marked and responded readily to rest and hospital treatment. The general arteriosclerosis and cardiac enlargement were moderate in degree; the neuroretinitis was mild, and renal functional studies revealed normal excretion. The patients improved and have enjoyed a restricted, but comfortable existence since they were dismissed from observation one year ago. The milder neuroretinitis found in these two cases is of less serious local and general import than the characteristic severe type. Vision was not affected and definite improvement occurred while the patient was under treatment. In such a retinitis, the lesion may disappear completely without residuals. These findings suggest that there are border line conditions, in which it is impossible to make a differential diagnosis between cases of early malignant and essential hypertension. In order to make the distinction, accurate observation during the subsequent courses of the disease appears to be necessary.

The determining local factor in the production of the severe retinitis is not known. It does not seem to depend on azotemia, as suggested by Opin and Rochon-Duvigneaud [10] and Leber,[11] nor on the severity of the preceding sclerosis in the retinal arteries, but may be associated, as Leber, and Volhard [12] and Schieck [13] suggest, with marked contraction in the smaller vessels. Its course is chronic and, once initiated, seems to be little influenced by local or general treatment. During its active stage, its effect on vision seems to depend on the amount of edema present in the macular region. In the majority of cases, vision is surprisingly good. If the patient lives long enough, the retinitis will

10. Opin and Rochon-Duvigneaud: Lésions comparées de la rétine et des autres organes chez les malades atteints de rétinite brightique; indications qu'elles fournissent sur la pathogénie de l'affection, Arch. d'opht. **24**:155-176, 1904.

11. Leber, T.: Die Netzhauterkrankungen bei Nierenleiden, Graefe-Saemisch Handb. d. ges. Augenheilk. **7**:913-926, 1915.

12. Volhard, F.: Die doppelseitigen hämatogenen Nierenerkrankungen, Berlin, Julius Springer, 1918, p. 576.

13. Schieck, F., and Volhard, F.: Netzhautveränderungen und Nierenleiden, Zentralbl. f. d. ges Ophthal. u. Grenzgeb. **5**:465-481, 1921.

probably heal ultimately, the end-results being varying degrees of post-neuritic optic nerve and retinal atrophy with corresponding slight or great loss of vision.

The results obtained in this study indicate that the finding of a serious neuroretinitis in cases of marked hypertension is of great prognostic significance. The ophthalmoscopic picture may be the earliest sign of the conversion of an essential into a malignant hypertension, and thus reveal a serious general vascular lesion when cardiac and renal function is surprisingly adequate. In such cases, it seems more reasonable to assume that the retinitis is dependent on the hypertensive vascular disease, rather than on a primary lesion of the kidney.

SUMMARY

Certain patients with severe neuroretinitis show little or no evidence of renal insufficiency. They have marked hypertension, moderate peripheral arteriosclerosis and cardiac hypertrophy, but their condition differs definitely from those with chronic diffuse glomerular nephritis. From the history, clinical and laboratory findings, and subsequent course, these patients appear to constitute a distinct clinical group.

THE METABOLISM OF GALACTOSE

I. THE THRESHOLD OF TOLERANCE IN NORMAL ADULTS*

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INTRODUCTION

This paper deals with certain of the results of a study, begun in 1916, on the diagnosis of certain endocrine disorders. The compilation of the data has been greatly delayed, but within the last two years, however, it has been possible to prosecute the studies actively, and this report embodies a small completed portion of the whole investigation. In evaluating the mass of data resulting from earlier animal experimentation, it was felt that the greatest caution was imperative in translating it into terms of human experience. By confining the studies to man, one major cause of uncertainty has been eliminated. While this has imposed certain limitations, the direct applicability of the results has brought ample compensation.

REASONS FOR SELECTION OF CARBOHYDRATE METABOLISM AS BASIS OF STUDY

With the selection of the subjects for experiment, the natural sequel was the determination of the tests to be applied. The field of so-called vital function testing offers a wealth of suggestions. With the great majority, if not with all, however, the goal has been to secure a test which should be sharply indicative of a single condition or of deviation in an individual functional capacity. With an apparently complex control of all bodily functions, this method of approach has led to the observation of numerous exceptions in the individual cases which have cast grave doubts on the specific validity of the test, and thus inhibited further investigation. If approached from the opposite point of view, however, those tests in which the largest number of factors may be operative offer the most attractive field of study. By the judicious selection of a variety of such measurements and the application of them, first to normal subjects and then to subjects in whom there existed some well defined, sharply characterized pathologic changes, the several variations produced by dysfunction might be ascertained, both in sense and in magnitude. Even granting a manifold and interdependent control of a given capacity, it seemed hardly probable that a series of widely

* Presented at the Seventeenth Annual Meeting of the American Society of Biological Chemists, Toronto, Dec. 29, 1922.

divergent tests should be under the same detailed and quantitative regulation. Thus, by establishing normal criteria, and by noting the influence exercised by well defined variations from the norm, it was hoped that sufficient data might be obtained to offer a basis for differential diagnosis. Further, a normal response to a given test produced by two opposing and mutually compensatory influences could hardly be produced throughout a series of tests, and so would be equally informative with wide divergences from the established normal.

It is hardly necessary to add that all tests must be quantitative, must be performed under rigidly controlled conditions, and that every precaution is observed to attain the highest degree of accuracy.

Assuming this point of view, the carbohydrate metabolism becomes a potentially most productive field for investigation. For several decades it has been recognized that the human body has a very definite limit to the amount of carbohydrate that can be metabolized under certain definitely circumscribed conditions, the so-called threshold of tolerance, and that there are numerous agencies which could affect this amount, either increasing or diminishing it.

Aside from the dominant influence of the internal secretions of the pancreas, severally, the liver, kidneys, the entire endocrine system and the central nervous system may or do all play some part. Further, aside from organic control, such factors as degree of muscular activity, temperature, nutrition and fatigue, have been reported as exercising influence, and, finally, certain states such as pregnancy, fever and neuroses of traumatic origin are also to be reckoned with. As the body receptivity varies with the several carbohydrates, it becomes necessary to designate the particular sugar which shall form the basis of the test.

CHOICE OF SUGAR

In the first place, the choice is directly limited to the hexose sugars. The adoption of disaccharids or polysaccharids is interdicted as introducing one more element of complication in a problem already far from simple. Of the several modes of administration, the oral route possesses several manifest advantages. Intraperitoneal and subcutaneous administration can be eliminated at once, rectal feeding represents a last resort rather than a method of election, and the intravenous technic of Woodyatt [1] and his co-workers, ingenious and highly interesting though it is, offers on the one hand certain obvious difficulties, and on the other, fails to throw light on certain of the physiologic functions which it was desired to study. With the field thus limited, the problem of selection

1. Wodyatt, R. T.; Sansum, N. D., and Wilder, R. M.: Prolonged and Accurately Timed Intravenous Injections of Sugar, J. A. M. A. **65**:2067 (Dec. 11) 1915.

is greatly simplified. Many of the conditions to be studied were reported in the literature as having greatly increased so-called tolerance thresholds. A few preliminary experiments demonstrated that with the large doses of glucose and of fructose, which many of the subjects would require, the digestive disturbances excited by test meals of heroic size would inevitably eliminate an appreciable number of observations. True, Miura [2] had exhibited massive doses of several carbohydrates with some measure of success, but personal experience showed the outcome to be highly precarious. Of the available sugars, then, only galactose remained.[3] This sugar, studied with others by several of the earlier students of carbohydrate metabolism, first attained the dignity of an independent diagnostic entity when suggested by Bauer [4] in 1906 as a test for liver function. A series of articles followed, chiefly clinical in character, in which the utility of galactose as a test meal was thoroughly canvassed.

From the mass of conflicting data one fact stood out saliently; namely, that the exciting dose of galactose was too small to cause the digestive disturbances which so marred the utility of the more common fructose and glucose. Further, galactose is not a foreign sugar in the sense that it forms no part of normal nutrition. Conjugated with glucose, it is the basis of carbohydrate metabolism of our earlier years, and is present in appreciable amounts in the diet of maturity.

The galactose assimilation in young children is of much interest in this connection. Excluding studies in which the presence of another sugar constitutes a disturbing element, several groups of feeding experiments are recorded. Schirokauer [5] with normal and lymphatic children, aged from 2 to 4 years, and Stern [6] with children aged from 4 to 8, all found results approximating adult levels. A most complete study is given in the work of Meyer and Stern,[7] who, with children ranging from 3 months to 7½ years of age, and with doses of galactose of from 10 to 60 gm. carried out a series of well devised and carefully controlled observations. The results show assimilation limits which are definitely comparable with those observed in the adult.

That galactose can build glycogen would seem to be the consensus of opinion. Brasch,[8] in a most interesting study of carbohydrate utilization, gives a very good review of the earlier literature. Perfusion

2. Miura: Ztschr. f. Biol. **32**:281, 1895.
3. The pentoses were of too doubtful a purity, too expensive and, in the main, too foreign to normal human metabolism to be taken in consideration.
4. Bauer: Wien. Med. Wchnschr. **56**:2537, 1906.
5. Schirokauer: Jarhrb. f. Kinderh. **79**:581, 1914.
6. Stern: Med. Klin. **15**:873, 1919.
7. Meyer and Stern: Arch. f. Kinderh. **68**:241.
8. Brasch: Ztschr. f. Biol. **50**:112, 1907.

experiments by Grube [9] with tortoise livers, and McGuigan [10] with muscle preparations, show direct utilization. Roubitschek,[11] and Hurwitz and Bloomfield [12] who, using lactose in experiments with animals poisoned with phosphorus and chloroform respectively, conclude that galactose is a former of glycogen. Most recently Mann and Magath [13] have shown that the revivifying effect of glucose on dogs, dying after liver extirpation, is duplicated in small measure by galactose.

Galactose, then, as a sugar not entirely foreign to the human economy, with so low an assimilation limit as to preclude nullifying digestive disturbance, of well defined chemical and physical properties, and apparently capable of direct absorption, was felt to be the most desirable of available carbohydrates. The results obtained with it have warranted amply the original selection.

THE "THRESHOLD OF TOLERANCE"

The significance and exact meaning of the term, "Threshold of Tolerance," require further discussion. Used as it is freely in contemporary literature to indicate two diverse, and, as I believe, mutually independent phenomena, definition must be made if grave confusion is to be avoided.

DEFINITION OF "TOLERANCE THRESHOLD"

The terms, "threshold of tolerance," has been applied severally to the following conditions:

1. The maximum amount of carbohydrate, and later, as the sugar-forming properties of other foods were recognized, the total food intake, which could be ingested by a sugar-free diabetic patient without causing a glycosuria.

2. The amount of a carbohydrate given under various conditions of control, which would excite a transitory but detectable melituria, the so-called assimilation limit.

3. The amount of carbohydrate which would produce an hyperglycemia just below the level of the so-called renal threshold.

In the first two, at least, the interpretation of a positive response has varied from the detection of the merest trace to the elimination of a definite number of grams. Since Jacobsen's [14] paper in 1913 gave a concrete magnitude to the term, "renal threshold," and particularly

9. Grube: Arch. f. d. ges. Physiol. **118**:1, 1907.
10. McGuigan: Am. J. Physiol. **21**:334, 1908.
11. Roubitschek: Deutsch. Arch. f. klin. Med. **108**:225, 1912.
12. Hurwitz and Bloomfield: Bull. Johns Hopkins Hosp. **24**:380, 1913.
13. Mann, F. C., and Magath, T. B.: Studies on the Physiology of the Liver, Arch. Int. Med. **30**:171 (Aug.) 1922.
14. Jacobsen: Biochem. Ztschr. **56**:471, 1913.

through the development of blood analytic methods, the blood picture, with the urine findings as a by no means necessary complement, has become the goal of investigation. In the present paper only the concept will be discussed which deals with the provocation of a melituria by an ingested sugar, and that sugar galactose. A preliminary survey of the literature gives meager assistance in determining the assimilation limit for the sugar in question. The more significant literature can be assembled in tabular form for purposes of discussion. Dealing first with so-called adult normal patients, in this instance cases without liver involvement, the data are found in Table 1. The results are somewhat

TABLE 1.—*Normal Patients. Liver and Thyroid Cases and Neuroses Omitted*

Author	Year	Dose	Number	+	−	Per Cent. +
Bauer [16]	1912	40	60	7[4]	53	12
Reiss and Jehn [21]	1912	40	12	1[3]	11	8
Hatiegan: Wien. klin. Wchnschr. **27**: 358, 1914	1914	40	4	0[1]	4	0
Maliwa [15]	1914	40	21	20[1]	1	95
Wagner [29]	1914	40	26	7[2]	19	27
Wörner and Reiss, Deutsch. med. Wchnschr. **40**: 907, 1914	1914	40	9	0[4]	9	0
Stern [6]	1919	40	6	5[1]	1	83
			138	40	98	29
Strauss [26]	1913	30	22	2[1]	20	9
Uhlmann [17]	1915	30	25	20[1]	5	80
			47	22	25	47
Frey: Ztschr. f. klin. Med. **72**: 383, 1911	1911	20	8	4[1]	4	50

1. Qualitative test. 2. > 1 gram. 3. > 2 grams. 4. > 3 grams.

diverse. Maliwa,[15] using a qualitative test as his criterion, finds 95 per cent. of his cases positive with 40 gm. while Bauer,[16] regarding a melituria of less than 3 gm. as of no significance, reports but 12 per cent. positive to the test.

Under apparently similar conditions, Stern [6] and Uhlmann [17] secured diametrically opposite results.

Many more data are available, but as they offer no better solution of the problem, in the interest of brevity extended discussion may be omitted.

Briefly summarized, it would seem as if the limits lay somewhere between 20 and 50 gm., with the middle figures of from 30 to 40 being the more probable. Von Noorden [18] places the so-called tolerance threshold at 20 gm. for orally administered galactose. Hirose,[19] in an

15. Maliwa: Med. Klin. **10**:762, 1914.
16. Bauer: Berl. klin. Wchnschr. **49**:1498, 1912.
17. Uhlmann: Arch. f. Verdauungskr. **21**:353, 1915.
18. von Noorden: Die Zuckerkrankheit, Berlin, Hirschwald, 1910.
19. Hirose: Deutsch. med. Wchnschr. **38**:1414, 1912.

excellently conceived and executed investigation, adopts 25, Strauss [20] prefers 30 as the most probable normal figure, and a group of investigators select 40 as the best available figure. The values found by Meyer and Stern [7] for young children, already quoted, are particularly significant in demonstrating the relative independence of the so-called threshold of age.

The criterion for a positive response is highly important, and in the earlier work showed pleasing variety. The apparent failure to recognize the significance of the carbohydrate paradox (Allen [21]) invalidates the significance of much of the published data. The appearance of detectable reducing material in an otherwise apparently sugar-free urine would seem to me to be a certain basis on which to gauge results. True, it establishes as the criterion the sensitivity of some qualitative chemical reagent. Further, numerous writers on this topic have treated the presence of "mere traces of urine sugar" in a very cavalier manner, and denied them all significance.

But the demonstration of detectable amounts of reducing substance after the administration of carbohydrate test meals in urines, otherwise uniformly negative to the test applied, indicates definitely that some change has taken place which can be referred only to one exciting cause. And with the selection of a reagent of proved sensitivity, reliability, and uniformity of behavior, a sound basis for comparison is established.

Some years ago, Benedict, Osterberg and Neuwirth [22] demonstrated the fact that there is a continuous leakage through the kidneys of some reducing substance or substances, and that the ingestion of any food caused an increase in the amount. That the urine always contained minute amounts of "sugar," had been recognized long before, but the authors in question gave a quantitative expression to the phenomenon which was most convincing. Further, they applied the term "glycuresis" to the increase in urine sugar resulting from ingestion of food substances in substitution for the more common, and possibly misleading "glycosuria."

More recently, a very comprehensive study of certain phases of carbohydrate metabolism by Folin and Berglund [23] has appeared, in which a most interesting and suggestive explanation is offered. As the results of their experiments, the authors conclude that "glycuresis represents the absorption and excretion of foreign, unusable carbohydrate

20. Strauss: Neurol. Centralbl. **32**:1281, 1913; Deutsch. med. Wchnschr. **39**:1780, 1913.

21. Allen: Glycosuria and Diabetes, 1913.

22. Benedict, S. R.; Osterberg, E., and Neuwirth, I.: J. Biol. Chem. **35**:217 (Aug.) 1918. Benedict, S. R., and Osterberg, E.: J. Biol. Chem. **55**:769 (April) 1923.

23. Folin, O., and Berglund, H.: J. Biol. Chem. **51**:213 (March) 1922.

materials. . . ." and that the "sugar of normal urine . . . . is a motley variety of carbohydrate products . . . . and derivatives." Benedict,[24] in a later paper contests this interpretation and reiterates his belief in the absence of any absolute tolerance for glucose in the individual. This belief has also been expressed recently by Rosenberg,[25] and is indeed shared by Folin and Berglund with regard to galactose and lactose, but not for glucose and fructose.

On the other hand, Benedict is of the opinion that certainly not more than 50 per cent., and usually not over 25 per cent. of urine sugar is glucose, an opinion also voiced by Maclean[26] as early as 1907. The work of Oppler[27] might be cited in this connection. This investigator finds in normal urine some 0.04 per cent. of a reducing, fermentable substance which is, however, optically inactive. He further concludes that glucose constitutes but a small part (about 25 per cent.) of the whole. Without citing further instances from the literature, it may seem to be fairly obvious that whatever individual differences of opinion may exist, all are agreed that a part, at least, of the reducing material is not glucose. The stress laid by Benedict on fermentable and nonfermentable moieties in the urine does not seem to me to be of such paramount importance as, on the one hand, other carbohydrates than glucose undergo this process, while on the other, there is always the possibility of the yeast introducing materials of a reducing nature which would still further cloud the issue. Another thought expressed by Benedict introduces the stereomeric relationships of α and β modifications of a given sugar, and reference is made to the recent work of Winter and Smith.[28] The drastic treatment to which these latter authors subjected their material may arouse some question of an extraneous and superimposed chemical effect. Even so, the lability of the simple carbohydrate molecule, the existence of the *gamma* modification, give food for thought in connection with the present problem.

After relatively large doses of galactose, several writers have identified galactose in the urine. Among others, Bauer[4] and Wagner[29] use mucic acid as a means of quantitating the output, yet most recently Bodansky,[30] working with dogs, was rarely able to detect galactose as such, although many grams of reducing material were present in the urine. The choice of his subjects may have some bearing on this apparent contradiction. Fortified by the positive mucic acid and osazone

24. Benedict, S. R.: The Detection and Estimation of Glucose in Urine, J. A. M. A. **57**:1193 (Oct. 7) 1911.
25. Rosenberg: Arch. f. exper. Path. u. Pharmakol. **93**:208, 1922.
26. Maclean: J. Biol. Chem. **2**:431, 1907.
27. Oppler: Ztschr. f. Physiol. Chem. **75**:71, 1911.
28. Winter, L. B., and Smith, W.: J. Physiol. **57**:101 (Dec.) 1922.
29. Wagner: Ztschr. klin. Med. **80**:174, 1914.
30. Bodansky, M.: J. Biol. Chem. **56**:387 (June) 1923.

(Reiss and Jehn[31]) findings of other observers, I have applied the Tollens test (phloroglucinol-hydrochloric acid) with uniformly positive results where reducing material was shown to be present by a sensitive copper reduction test (Benedict's).

To summarize the foregoing, the so-called "normal sugar" of the urine is generally regarded as containing but small amounts of glucose, if indeed there is any. Ingestion of appreciable amounts of the common sugars may show small increases in this "glycuresis," or better, "melituresis;" the addition of other food stimulates a larger excretion, but in all instances the amounts are absolutely small. With the ingestion of certain larger quantities of sugar, the amounts severally dependent on the character of the sugar, the conditions of administration, and the metabolic relation of the subject, there is at once a notable increase in the amount of the "sugar" elimination. It becomes qualitatively detectable in the urine, and a part, at least, of the reducing body thus appearing, is identical with that which was ingested. Further, the ingestion of slightly smaller amounts fails to produce any of the above phenomena.

It would certainly seem here as if there was some definite transition, an inauguration of new, rather than a quantitative increase of old processes. The Folin-Berglund interpretation of the character of urinary "normal sugar," and of the definite but small increases observed under the stimulus of food or sub-tolerance doses of carbohydrate, would seem to give a most workable explanation of the whole mechanism under discussion.

When one considers the extreme difficulty of freeing such stable compounds as inorganic salts from the least trace of impurity, the impossibility of purifying such labile substances as the carbohydrates from contaminants is patent. A procedure of sufficient drasticity to remove one offending material may well give rise to yet larger quantities of another.

For purposes of convenience, then and with full recognition of the incompleteness of the experimental background for certain assumptions made, in the following discussion certain conventions will be adopted.

First, the term "super tolerance dose" will be used to designate that amount of galactose, which, administered to an adult in basal condition (i. e., resting and fasting) in water, in a concentration of from 10 to 20 per cent., will produce a transitory melituria demonstrable by a sensitive and dependable copper reduction test (Benedict's).

Second, the term, "sub tolerance dose," will be used equally to designate that dose, a few grams less than the foregoing, which by like administration fails to produce any demonstrable melituria.

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31. Reiss and Jehn: Deutsch. Arch. f. klin. Med. **108**:187, 1912.

SCOPE OF INVESTIGATION AND METHODS EMPLOYED

From the analysis of the earlier work on galactose feeding, it is obvious that nothing was definitely known concerning the real assimilation limit of this sugar. To standardize the present work and establish criteria for later comparisons, the first phase of the study was confined to investigations with so-called normal individuals

Based on the experience of many years, I feel that a word of caution is not misplaced at this point. In studies of this character, the investigator usually enlists the services of volunteer aids, in many instances students, nurses and colleagues. These individuals, living their normal lives and following their respective vocations, are assumed to be normal, in other words, average. That this assumption is not always warranted any worker in this field will testify. In the present study, several of the subjects, during the course of preliminary standardization, demonstrated evidences of functional or organic derangement. For example, two house officers volunteering as subjects, were found to be cases of endocrine hypofunction. In both instances they subsequently stated that they had known themselves to be somewhat at variance from the average, but had attached no importance to it. A still more striking case was observed in another patient, who was studied unknowingly during the development of nephritis. Other cases, as will be brought out in the subsequent discussion, were probably not strictly normal, but as no definite aberration could be detected, they are included in the list. Unsuspected renal glycosurias may be a potent source of error in work of this character unless due precautions are observed and each case subjected to a thorough preliminary testing.

During the earlier part of the work certain highly informative tests now in current use were unavailable. As a preponderance of the subjects here reported did not receive these additional observations, only that part which were common to the entire group will be considered here.

The subjects comprising this group were, in the main, presumably healthy young men and women, either medical students or nurses and interns connected with the hospital. A few other volunteers from outside were also included.

Work of this character is only significant when it is conducted under uniform and carefully controlled conditions, and in which the measurements are quantitative in character. Needless to say, in all analytic procedures the highest obtainable accuracy is the only factor to be considered. To unify external conditions, so far as possible, the subjects all lived at the hospital during the period of study.

To insure approximate nutritional equilibrium, a standard diet was outlined and followed. The subjects received not less than 6 gm. of

carbohydrate, 1.66 gm. of protein, and a gross energy intake of not less than 45 calories per kilogram of body weight. Further, as these studies were in no sense exact metabolism investigations, every effort was made to render the diet as varied and palatable as possible. The necessity for exact analysis of the food intake was not operative, and so permitted a most desirable elasticity in the choice of viands. Food values, computed from Locke's [32] compilation, were sufficiently accurate for the purpose. I should like to stress the importance of this aspect in experiments of any duration. The average individual, indifferent alike to the urge of pure science and the enthusiasm of the dietary propagandist, is influenced unfavorably, both directly and indirectly, by the continuance of an unvaried and potentially unpalatable diet.

The standard daily regimen can be presented most succinctly in tabular form.

TABLE 2.—*Schedule*

First day, 7:00 a.m.	Start collection of first 24-hour urine
7:30 a.m.	Breakfast. Diet begins. Physical examination
Second day, 7:00 a.m.	Complete first 24-hour urine. Miscellaneous tests including phenolsulphonephthalein
Third day	Collect second 24-hour urine. Nitrogen partition
Fourth day	Repeat second day
Fifth day, 5:00 a.m.	Empty bladder. Ingest 30 or 40 gm. galactose in from 10 to 20 per cent. solution
7:00 a.m.	Collect urine G1
9:00 a.m.	Collect urine G2
9:05 a.m.	Breakfast
11:00 a.m.	Collect urine G3
1:00 p.m.	Collect urine G4
1:05 p.m.	Dinner
Sixth day	Repeat fifth day, changing dose of galactose by ±10 gm.
Nth day	Collect third 24-hour urine. Nitrogen partition II
(N + 1)th day	Repeat second day. Diet ends. 12:30 p.m. dinner

The significance of some of the tests given in the foregoing may be touched on briefly. The phenolsulphonephthalein and the careful urine examinations were used as indexes of kidney permeability and the nitrogen partition gave information concerning liver and, by implication, kidney function. All urines were examined for abnormal constituents, while the total nitrogen of the first urine was determined for comparison with those later secured, to ascertain if the prescribed dietary regulation entailed any profound modification of the subjects' usual habitude. As will be seen from the schedule, graded doses of galactose were given until the dose exciting melituria had been determined. In all urines giving a positive response to the qualitative sugar test, the amount of reducing material was estimated quantitatively, and as before stated, the Tollens test applied. Space forbids the discussion of the analytic details of the numerous methods used. It may be said generally that the methods selected were those of proved worth, accuracy being the sole criterion. The galactose test may be permitted a more extended statement.

32. Locke: Food Values, New York, D. Appleton & Company, 1911.

In all of these experiments only galactose of a demonstrated purity was used. In the earlier tests, the material was obtained from several sources; latterly, the Pfanstiehl product of highest purity has been used exclusively. All were tested thoroughly for purity and doubtful materials were rejected. For the simple assimilation test the technic of administration is as follows: Either at 5:00 a. m. or 7.00 a. m. (depending on the other tests to be applied), the patient empties the bladder, the urine being tested for the presence of reducing bodies. The

TABLE 3.—*Men*

	Case	Physical: Age, Years	Physical: Weight, Kg.	Phenolsulphonephthalein %: First Hour	Phenolsulphonephthalein %: Second Hour	Phenolsulphonephthalein %: Total	Galactose Tolerance: +	Galactose Tolerance: 0	Galactose Tolerance: Elim.
A	1	33	64.3	45	18	63	30	20	<1.00
	4	30	65.0	37	24	61	20	10	0.64
	16	31	65.8	43	26	69	30	20	2.10
	5	30	80.2	29	21	50	30	20	1.15
	6	27	68.3	46	19	65	40	30	0.65
	7	27	67.0	56	19	75	20	10	0.39
	8	39	83.2	—	—	50	40	30	0.39
	9	31	69.4	33	21	54	30	20	0.80
	10	21	65.8	45	32	77	40	30	1.50
	11	30	71.0	49	31	80	30	20	1.20
	12	20	69.8	39	32	71	30	20	0.39
	13	20	58.5	59	20	79	40	30	0.33
	14	23	54.8	53	17	70	30	20	1.43
	15	26	56.4	49	23	72	20	15	0.78
	18	28	74.3	49	29	78	30	20	0.90
	19	24	71.6	45	33	78	30	20	1.18
B	16	70	67.1	19	25	44	40	30	1.74
	38	25	58.0	42	35	77	30	20	0.55
				Women					
A'	1	22	60.4	44	21	65	20	20	1.00
	2	31	56.8	35	24	59	40	30	<1.0
	3	28	50.0	29	25	54	40	30	<1.0
	6	23	58.9	56	16	72	40	30	<1.0
	7	24	55.2	40	18	58	50	40	0.22
	9	20	52.5	25	22	47	50	40	2.50
	10	20	49.2	36	15	51	50	40	2.50
	11	19	79.7	37	25	62	50	40	0.35
	12	23	47.0	34	29	63	30	20	1.60
	14	24	52.7	40	22	62	30	20	1.91
	15	26	89.1	38	17	55	40	30	0.25
	16	25	54.8	24	28	52	30	20	0.96
	18	29	74.3	25	24	49	50	40	2.14
B	14	28	66.3	49	21	70	30	20	0.42
	19	52	47.6	61	24	85	40	30	0.60
	31	39	62.9	41	34	75	40	30	0.46

test meal of 30 gm. of galactose for men and 40 gm. for women is administered orally in a cold aqueous solution of from 10 to 20 per cent. The use of lemon or orange juice, as frequently indicated by other observers is carefully avoided. Aside from the fact that it is unnecessary, it introduces a factor of complication in adding varying amounts of foreign sugar. Urine is collected in two two-hour periods, and four hours after the administration of the test meal the subject arises and breakfast is given. The urines are tested qualitatively for the presence of reducing bodies by the Benedict qualitative solution, and where response is positive the amount is determined by the Bene-

dict [3] quantitative titration. The slower reduction time of galactose does not introduce a seriously disturbing factor by this method. During the earlier tests, a third and fourth two-hour collection of urine was made, but as they were found invariably to be negative, in the later measurements the practice was discontinued.

RESULTS AND INTERPRETATION

Partial results of the study are compiled in Table 3. From the serial numbers designating the subjects, it will be seen that certain cases have been omitted. The basis for such omissions were varied, ranging from the nephritis of Case 17A', already alluded to, and the development of a grave condition which ended fatally in Case 2A, to the proven independability of the subject, as was the case with Case 8A'. As the thesis was the evaluation of the probable threshold of tolerance, so-called, I felt warranted in discarding those cases where demonstrable

TABLE 4.—*Summary of the Collected Data*

	Physical		Galactose Test		
	Age, Years	Weight, Kg.	Positive, Gm.	Negative, Gm.	Excreted, Gm.
High:					
Male	70	83.2	40	30	2.10
Female	52	89.1	50	40	2.59
Low:					
Male	20	54.8	20	10	0.33
Female	19	47.0	30	20	0.25
Average:					
Male	29	67.2	31.1	21.3	0.95
Female	27	59.8	40.0	30.0	1.12

pathology negatived the normalcy of the case, or where the authenticity of results could be proven lacking. The cases from Series B were concerned in another study but were suitable for inclusion here.

On the other hand, a few cases were included of which I am suspicious, but as concrete evidence of aberrant function was lacking, they were retained in the group. Case 8A falls definitely under suspicion. Certain observations unrecorded here are found to be characteristic apparently of certain endocrine conditions. It is to be greatly regretted that at the time of this test the basal metabolic rate could not be determined. Of the five males showing a positive response at 40 and negative at 30, two, Case 10A and Case 16B eliminate amounts of reducing material, which would show that the probable threshold in the conventional sense is nearer the lower than the higher figure. Similarily, of the five women with an upper limit of 50 gm., three fall in the same category.

As has already been pointed out, the term, "normal," in such connection implies "average" as its true meaning. For this reason summations of the collected data are significant.

Such a condensation is given in Table 4.

Barring the basic observation that there seems to be a fairly well indicated value for the tolerance of galactose in so-called normal adults, as stated in the foregoing, it is not the purpose of this paper to consider the diagnostic aspects of this work. Bearing on the variations from the calculated average of individuals in the present group, it may be said that endocrine cases have been observed showing much greater deviation from the normal. In male cases the positive dose was severally as high as 80 and as low as 13 gm., while with women a low limit of 5 gm. has several times been observed, and in one case, 100 gm. of galactose was administered without exciting a melituria. In the light of these facts, the variations here observed lose something of a disturbing significance. The most striking fact here elicited is the evident difference in this level, which must be referred to sex. While I could wish for a larger number of observations on which to base a conclusion, other and later work bears out this conclusion in no unmistakable manner. Pending the completion of investigations now under way, no final conclusion may be drawn, but the fact as observed holds certain attractive possibilities for speculation.

Woman, in her adult years, entertains within her organism a specific galactose mechanism which, so far as is known, is lacking in man. A power of synthesis, of storage and of conjugation of galactose is inherent in the female mammary glands. Grouped among the secondary sex characteristics, coming into development only when sex manifests itself in functional readjustments, it forms a specific point of difference with a specific galactose contact. Whatever the true explanation may be found to be, the fact is certainly interesting and novel.

Certain other aspects may be commented on briefly. In many of the recent studies, the tolerance dosage has been allocated to a relationship with body weight. The Janney [33] technic calls for 1.75 gm. of glucose per kilogram of body weight. That this is not warranted in the case of galactose is clearly indicated by the data given here. Relative independence of body weight and tolerance threshold are here manifest. Nor has it been possible to establish other biometric relationship. A comparison of dosage with area calculated by the well known DuBois [34] equation, shows an equal independence. This is repeated in basal metabolism computations (not recorded here), as of course would be expected from the standards involved in such calculations. Age in adults also seems to be without basic influence.

In short, the amount of galactose to be designated under the conventions adopted, as the threshold dose, seems to be a quantity approximat-

33. Janney, N. W., and Isaacson, U. T.: The Blood Sugar in Thyroid and Other Endocrine Diseases, Arch. Int. Med. **22**:160 (Aug.) 1918.

34. DuBois, D., and DuBois, E. F.: Clinical Calorimetry, Arch. Int. Med. **17**:863 (June) 1916).

ing a constant value in healthy adult individuals, and greatly influenced solely by sex among the several biologic factors of potential variation. Later unpublished observations show that with women, the menopause may cause a lowering in the observed level, a fact of supporting significance.

SUMMARY

The results of this study may be summarized briefly as follows:

1. The significance of the term "threshold of tolerance," for carbohydrates, and the assimilation limit in terms of urine findings is defined.

2. Certain necessary control limitations in the application of a provocative melituria test are indicated, and the technic of a test using galactose is described.

3. By means of this test, the conventionally defined threshold of tolerance for groups of normal adult men and women is studied and the results reported.

4. The dose exciting melituria is influenced little, if at all, by age, weight, body area or certain other biometric factors.

5. It is found to be apparently directly dependent on sex, and the influence of the mammary glands in woman is suggested as a possible explanation.

6. The average "tolerance dose" for man is found to be 30 gm. and for woman 40 gm.

THE MUSCULAR EFFICIENCY OF PATIENTS WITH DIABETES MELLITUS*

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The results of a study on the muscular efficiency of a group of patients with diabetes mellitus are presented. Ordinarily, in following cases it is customary for the patient's physician to examine the blood and urine for sugar by quantitative methods, to measure objectively loss or gain in weight and tolerance but to rely on symptoms for a record of loss or gain in physical strength and sense of well-being. Since physical weakness is one of the commonest symptoms of diabetes, and one of its most devastating features from an economic point of view, we thought it important to determine by quantitative methods how weakening a process diabetes may be and to find out what modern methods of treatment can accomplish in the physical reconstruction of sufferers with this illness.

Williams [1] has already studied the problem of muscular efficiency in diabetes by means of the Colin dynamometer. He has shown that diabetic patients tend to be weaker than normal persons and that there is a direct relationship between their food tolerance and muscular vigor. Miles [2] and Root,[3] attacking the question from a somewhat different angle, have shown that the average diabetic patient is not physically fit, using body weight as an index, and furthermore is below normal mentally to various psychologic tests, approaching but not reaching a normal mentality with treatment. On the whole, therefore, it becomes apparent that before the discovery of insulin treatment even the best treated diabetic patient usually carried a handicap in his struggle for existence of a measurably diminished physical and mental efficiency, and too often was compelled to face a slowly progressive course of physical and mental deterioration.

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* This paper is No. 20 of a series of studies in metabolism from the Harvard Medical School and allied hospitals. The expenses of this investigation have been defrayed (in part) by a grant from the Proctor Fund of the Harvard Medical School for the study of Chronic Diseases.

1. Williams, J. R.: The Effect of Undernutrition on Muscular Force, Arch. Int. Med. **20**:399-408 (Sept.) 1917.

2. Miles, W. R., and Root, H. F.: Psychologic Tests Applied to Diabetic Patients, Arch. Int. Med. **30**:767-777 (Dec.) 1922.

3. Root, H. F., and Miles, W. R.: Physical Measurements of Diabetic Patients, J. Metabolic Res. **2**:173-197 (Aug.) 1922.

We have studied the muscular efficiency of a group of twenty-three diabetic patients during the last year, obtaining observations in several cases on the effect of prolonged treatment on strength, using a group of normal persons by way of control. To estimate strength we have used the resistance strength test of Lovett and Martin,[4] a method which we have found simple and accurate. Martin,[5] also, has used the method satisfactorily in studying certain problems of industrial medicine, as has Smith [6] in studies on the strength of soldiers with effort syndrome. For a description of the details and principles of the method we refer to Martin's [7] comprehensive description of it. In brief, the test measures the maximum resistance which various selected muscle groups offer against stretching. From the data so obtained it is possible to calcu-

TABLE 1.—*The Strength of Eighteen Normal Men*

Number	Age	Height, Cm.	Weight, Kg.	Total Calculated Strength, Kg.	Strength-Weight Ratio
1	30	180	76	2,000	26.6
2	29	171	60	1,600	26.6
3	24	180	78	1,880	23.6
4	29	173	57	1,320	23.0
5	27	166	57	1,290	22.6
6	23	172	62	1,350	21.7
7	24	180	64	1,370	21.6
8	42	170	48	1,030	21.6
9	25	177	76	1,630	21.4
10	30	175	70	1,480	21.0
11	22	169	61	1,270	20.7
12	30	174	63	1,300	20.5
13	21	189	89	1,810	20.3
14	23	185	64	1,270	19.9
15	29	182	74	1,450	19.6
16	23	176	84	1,540	18.4
17	26	180	66	1,120	17.3
18	37	181	78	1,230	15.7
Average				1,440	21.2

late the entire muscular strength of the body. The result is expressed in kilograms of total strength or perhaps more accurately in the ratio between strength and weight. We have used for muscle examples those muscle groups advocated by Martin in the abbreviated strength test and used by Smith in his study, namely: the right and left pectorals, the right and left wrist flexors, the right and left forearm flexors, the right and left thigh adductors and the right and left thigh abductors.

4. Lovett, R. W., and Martin, E. G.: The Spring Balance Muscle Test, Am. J. Orthop. Surg. **14**:415-424 (July) 1916.

5. Martin, E. G.: Strength Tests in Industry, Pub. Health Rep. **35**:1895-1926 (Aug. 13) 1920.

6. Smith, B.: The Possibilities of Physical Development in Cases of Effort Syndrome by Means of Graded Exercises, Arch. Int. Med. **24**:321-331 (Sept.) 1919.

7. Martin, E. G.: Tests for Muscular Efficiency, Physiological Rev. **1**: 454-474 (July) 1921.

Table 1 records our observations on single strength tests in a group of normal men. We found that the total strength, as estimated by a single determination with the method in our hands, varied between 1,100 and 2,000 kg. with an average of 1,441. The strength-weight ratio varied between 26.6 and 15.7 with an average of 21.2. Martin and Rich,[8] studying the strength of a large number of normal men with this method, found total strength figures varying from 910 kg. to 2,640 kg. with an average of 1,800 kg. and strength-weight ratios ranging from 19 to 37 with an average of 26.6. Our normal men, therefore, were weaker on the whole than the larger series of Martin and Rich. Our subjects were house officers and medical students, while Martin and Rich's were perhaps in better training as they included college

TABLE 2.—*The Strength of Eighteen Normal Women*

Number	Age	Height, Cm.	Weight, Kg.	Total Calculated Strength, Kg.	Strength-Weight Ratio
1	26	148	39	730	18.7
2	24	166	54	940	17.4
3	23	159	61	1,060	17.3
4	22	175	57	950	16.6
5	21	163	51	810	16.0
6	20	169	70	1,120	16.0
7	21	170	62	950	15.4
8	21	160	52	810	15.4
9	22	167	53	790	14.9
10	20	162	48	720	14.9
11	21	166	52	760	14.6
12	19	169	54	760	14.1
13	20	159	54	750	13.9
14	28	167	70	930	13.3
15	23	159	53	709	13.1
16	21	166	62	795	12.8
17	20	164	59	750	12.7
18	22	168	67	780	11.7
Average				840	14.9

students and recent army recruits. Furthermore, their figures are the average of more than one determination. However, our men were strong enough to work hard; therefore we have used our figures as a normal base line and have compared the strength of our male diabetic patients with our average normal male strength figure and strength-weight ratio.

Table 2 records similar observations on single strength tests in a group of normal women. We found that the total strength varied between 700 and 1,100 kg., with an average of 839. The strength-weight ratio varied between 11.7 and 18.7 with an average of 14.9. Here again our subjects were weaker than Martin's 116 factory workers, who had an average strength of 900 kg. and strength-weight ratio of

8. Martin, E. G., and Rich, W. H.: Muscular Strength and Muscular Symmetry in Human Beings, Am. J. Physiol. **47**:29-42 (Sept.) 1918.

16.3, and considerably weaker than Mosher and Martin's [9] forty-five college women, with an average strength-weight ratio of 22.5.

Our women were pupil nurses, secretaries, or technicians who volunteered to act as controls. Some were on night duty at the time the test was made, so that loss of sleep may have been a factor in causing our low figures. However, all were strong enough to carry on their routine work; therefore we have used our figures as a normal base line, and have compared the strength of our female diabetic patients with our average normal female strength figure and strength-weight ratio.

Since one of the main objects of our study was to make repeated strength tests on patients for a reasonable period of time, it was necessary to determine the variations in strength occurring in normal persons from day to day as detected by the method. For this purpose we made daily strength tests for a month on each of five normal men, and weekly strength tests for a period of six weeks on each of seven other normal

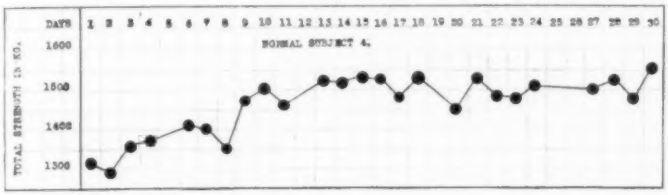

Chart 1.—The daily variation in strength of a normal man.

men. In the daily strength tests we found a tendency for total strength to increase for the first few determinations, and thereafter to remain at a fairly constant level. In the weekly strength tests we found a slight variability, but no tendency for the graph to deviate to any great extent from a straight line. We found, however, appreciable temporary variations in strength caused by loss of sleep, minor infections, and exercise before the test was made. Typical examples of these points are tabulated.

Chart 1 records the strength curve of a normal subject, and is composed of twenty-five determinations made during the course of a month's observation. During the first nine days there was a progressive rise in strength until a constant level was gained. Subsequently, the strength varied but little until the experiment was ended. The initial rise in strength was in all probability due to practice, while the subsequent straightness of the line illustrates the limits of constancy which are obtainable by the method when the test is used on a trained subject. All determinations were within 12 per cent. of the mean, showing that the technical errors of the method are not too great for clinical purposes.

9. Mosher, C. D., and Martin, E. G.: The Muscular Strength of College Women, J. A. M. A. **70**:140-142 (Jan. 19) 1918.

Chart 2 records details from the strength curves of two normal subjects to illustrate the effect of infection, exercise, and loss of sleep on strength. Each of these factors caused an appreciable though temporary loss in strength. The chart is plotted to magnify the variations in strength which were observed.

From such evidence, therefore, we believe that Lovett and Martin's method of testing strength is sufficiently accurate for clinical purposes. By using it, we were able to establish a normal base-line of strength with which to compare the strength of patients with diabetes, and we were able to show that strength in a normal individual remains relatively constant when followed for any length of time although it is modified temporarily by such factors as loss of sleep, infection or exercise. We

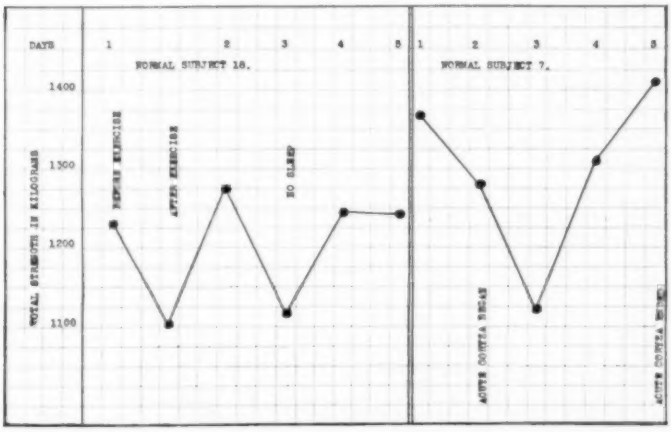

Chart 2.—The effect of exercise, loss of sleep, and an acute infection on strength.

have used as an average figure of normal strength our figures of 1,440 kg. for men and 840 kg. for women; we have considered the normal strength-weight ratio of men 21.2 and of women 14.9.

Table 3 records single strength tests on a group of fourteen adult male diabetic patients. These strength tests were made, with one exception, shortly after the patients entered the hospital and before treatment had been followed for any length of time. Case 5 was one of Joslin's [10] patients, who has faithfully carried out treatment under his guidance for ten years. While the diabetic group as a whole was older and less heavy than the normal group, a comparison between the two

10. Joslin, E. P.: The Treatment of Diabetes Mellitus, Philadelphia, Lea and Febiger, Ed. 3.

brings out two important features. The average strength of the diabetic group was considerably less than normal, ranging from 760 to 1,430 kg. in contrast to the normal range of between 1,100 and 2,000 kg. Moreover, the diabetic patients were not only weak from loss of body tissue but tended to be weaker than normal in proportion to their weights, because the average diabetic strength-weight ratio was 18.8 with a range

TABLE 3.—*The Strength of Fourteen Diabetic Men*

Number	Age	Height, Cm.	Weight, Kg.	Total Calculated Strength, Kg.	Strength-Weight Ratio	Duration of Diabetic Symptoms
1	30	165	47	1,210	25.8	3 years
2	16	170	45	1,140	25.0	2 years
3	42	175	63	1,430	22.7	4 years
4	26	178	58	1,300	22.5	8 months
5	40	177	50	1,020	20.4	10 years
6	43	168	56	1,010	18.0	4 years
7	37	177	71	1,270	17.9	1 month
8	48	183	65	1,160	17.8	2 years
9	38	172	49	850	17.5	9 months
10	28	170	49	850	17.3	5 months
11	22	174	60	1,020	16.9	2 years
12	36	169	53	760	14.2	3 years
13	53	176	56	775	13.9	7 years
14	52	177	50	690	13.9	5 years
Average				1,000	18.8	

of from 13.9 to 25.8, in contrast to the normal average of 21.2 with a range between 15.7 and 26.6.

Five of these patients (Cases 9, 10, 12, 13 and 14) when we first saw them had less than 60 per cent. of a normal man's strength. This gives an idea of how weakening a process diabetes may become. Of these five patients, two died within a few months from the time we first saw them, two have improved remarkably and we have lost track

TABLE 4.—*The Strength of Five Diabetic Women*

Number	Age	Height, Cm.	Weight, Kg.	Total Calculated Strength, Kg.	Strength-Weight Ratio	Duration of Diabetic Symptoms
1	41	165	47	840	18.0	4 months
2	21	156	38	625	16.5	18 months
3	18	160	42	620	14.6	4 months
4	33	160	40	540	13.5	8 months
5	23	165	52	600	11.5	3 months
Average				645	14.8	

of the other one. The rapidity with which the two fatal cases succumbed despite the use of insulin, suggests that extreme physical weakness may be of prognostic significance.

The duration of symptoms appeared to have little to do with the amount of weakness measured. Rather, one gets the impression that the most neglected patients grew weak most rapidly and that the ones that made any attempt to take care of themselves conserved strength the longest.

Table 4 records single strength tests on the five diabetic women of the series. The findings in this group are similar to those obtained in the men. The average age of the patients was greater and the weight less than that of the normal group. The average diabetic strength was considerably less than normal, ranging from 540 to 840 kg., in contrast to the normal range of between 730 and 1,120 kg. One interesting difference between the diabetic men and women, however, was the apparent normality of the diabetic women's strength-weight ratio. The average strength-weight ratio of the diabetic women was 14.8 against the normal variation of 14.9. The variations encountered ranged between 11.5 and 18.0, while the normals variation ranged between 11.7 and 18.7. This finding may be accidental, as the series was very small.

Systematic exercise is usually considered to be a part of the treatment of diabetes. On this account we attempted to find out whether the diabetic patients' physical weakness was evenly distributed, or whether it was due to an exaggerated weakness of any specific muscle

TABLE 5.—*Composite Strength Test of Normal Men*

Age 27, Height 176 Cm., Weight 68 Kg., Total Calculated Strength 1,430 Kg., Strength-Weight Ratio 21.0.

Muscles		Strength, Kg.	Per Cent. Total Strength
Pectoral	Left	34	2.4
	Right	36	2.5
Wrist flexor	Left	22	1.5
	Right	22	1.5
Forearm flexor	Left	32	2.2
	Right	31	2.2
Thigh abductor	Left	19	1.3
	Right	20	1.4
Thigh adductor	Left	18	1.3
	Right	19	1.3

group which might be overcome by appropriate physical therapy. Martin has shown that the sum of the strengths of the individual muscles tested constitutes in men 17.7 per cent., and in women 18 per cent., of the entire strength as found by this system of testing. By making a composite strength test from the individual subjects of the series, and analyzing the relative distribution of strength, we were able to obtain data on the distribution of the strength of normal and diabetic persons.

Table 5 records a composite strength test made from the eighteen normal men of Table 1. The resulting man was aged 27, 176 cm. (5 feet, 9½ inches) tall and weighed 68.2 kg. (150 pounds) in his clothes. His total strength was 1,430 kg. and his strength-weight ratio was 21. Of his strength, 4.9 per cent. came from his pectoral muscles, 3 per cent. from his wrist flexors, 4.4 per cent. from his forearm flexors, 2.7 per cent. from his thigh abductors and 2.6 per cent. from his thigh adductors.

Table 6 records a similar composite strength test made from the fourteen diabetic men of Table 3. The resulting man was aged 37, 174 cm. (5 feet, 8¾ inches) tall and weighed 54.8 kg. (121 pounds) in his clothes. His total strength was 1,020 kg. and his strength-weight ratio was 18.6. Of his strength, 4.6 per cent. came from his pectoral muscles, 3.3 per cent. from his wrist flexors, 4.7 per cent. from his forearm flexors, 2.7 per cent. from his thigh abductors and 2.5 per cent. from his thigh adductors.

TABLE 6.—*Composite Strength Test of Diabetic Men*

Age 37, Height 174 Cm., Weight 55 Kg., Total Calculated Strength 1,010 Kg., Strength-Weight Ratio 18.4.

Muscles		Strength, Kg.	Per Cent. Total Strength
Pectoral	Left	22	2.2
	Right	24	2.4
Wrist flexor	Left	16	1.6
	Right	17	1.7
Forearm flexor	Left	23	2.3
	Right	24	2.4
Thigh abductor	Left	12	1.2
	Right	15	1.5
Thigh adductor	Left	12	1.2
	Right	13	1.3

In other words our normal man, according to medical-actuarial statistics was about 8 pounds (3 kg.) under standard weight for one of his years and size, while our diabetic man was about 40 pounds (18 kg.) under standard weight. Besides being undernourished, the diabetic man was weaker than normal because he was only about 70 per cent. as strong as the younger normal man, and this weakness did not depend on

TABLE 7.—*Composite Strength Test of Normal Women*

Age 21, Height 164 Cm., Weight 57 Kg., Total Calculated Strength 840 Kg., Strength-Weight Ratio 14.7.

Muscles		Strength, Kg.	Per Cent. Total Strength
Pectoral	Left	18	2.1
	Right	19	2.3
Wrist flexor	Left	13	1.5
	Right	13	1.5
Forearm flexor	Left	18	2.1
	Right	19	2.3
Thigh abductor	Left	14	1.7
	Right	14	1.7
Thigh adductor	Left	12	1.4
	Right	12	1.4

undernourishment solely because his strength-weight ratio was diminished. He was not weak, however, in any specific muscle group, because the contributions of the muscle groups studied to the total strength were essentially the same as in the normal.

Table 7 records a composite picture of our group of normal women. The resultant subject was aged 21, 164 cm. (5 feet, 4¾ inches) tall

and weighed in her clothes 56.6 kg. (124 pounds). Her total strength was 845 kg. and her strength-weight ratio was 14.9. Of her strength 4.3 per cent. came from her pectoral muscles, 3.1 per cent. from her wrist flexors, 4.3 per cent. from her forearm flexors, 3.4 per cent. from her thigh abductors and 2.8 per cent. from her thigh adductors.

Table 8 records a composite strength test from the diabetic women. The resultant subject was 27 years old, 161 cm. (5 feet 3½ inches) tall and weighed in her clothes 43.8 kg. (91 pounds). Her total strength was 645 kg. and her strength-weight ratio was 14.7. Of her strength, 4.4 per cent. came from her pectoral muscles, 3.4 per cent. from her wrist flexors, 4.6 per cent. from her forearm flexors, 3.0 per cent. from her thigh abductors, and 2.7 per cent. from her thigh adductors.

TABLE 8.—*Composite Strength Test of Diabetic Women*

Age 27, Height 161 Cm., Weight 44 Kg., Total Calculated Strength 650 Kg., Strength-Weight Ratio 14.8.

Muscles		Strength, Kg.	Per Cent. Total Strength
Pectoral	Left	14	2.2
	Right	14	2.2
Wrist flexor	Left	11	1.7
	Right	11	1.7
Forearm flexor	Left	15	2.3
	Right	15	2.3
Thigh abductor	Left	10	1.5
	Right	10	1.5
Thigh adductor	Left	9	1.4
	Right	8	1.2

Our normal woman was 4 pounds (1.8 kg.) under standard weight for one of her age and size. Our diabetic woman was 35 pounds (15.9 kg.) under standard weight for one of her age and size. Our diabetic woman, therefore, was undernourished and weak although she was not weak out of proportion to her weight, having a normal strength-weight ratio. There was no specific muscle group weakness, because the contribution of the muscle groups studied to total strength was essentially similar in both groups.

From these data it is suggested that the best form of physical therapy for a diabetic patient is any general form of exercise directed toward improving the entire physique. Since the diabetic patients' weakness is not due to the weakness of any specific group of muscles, massage, mechanotherapy or exercise directed to any single muscle or small group of muscles is not indicated.

There may be secondary factors causing the weakness of a diabetic person other than the primary factor of prolonged undernutrition and underweight. This is suggested by a comparison of the strength test of Case 8 of the normal men with Case 5 of the diabetic men. The data are recorded in Table 9.

The normal subject was 50 pounds (22.7 kg.) under standard weight for one of his years and size, while the diabetic subject was 58 pounds (26 kg.) under standard weight. Both had the same amount of total strength and essentially normal strength-weight ratios. The normal man was stronger in the pectoral and forearm muscles than the diabetic subject, while the diabetic man compensated for this weakness by being stronger than the normal man in his leg muscles. The normal man had been thin all his life and was able to lead a very normal and productive life as a physiologist. The diabetic patient had been under treatment for ten years, unable to do a full day's work and gradually losing weight but keeping up strength by systematic exercise. The two men were in a way comparable as physical specimens at the time of the strength test, for it is needless to say that both were normal to physical

TABLE 9.—*Comparison in Strength Between a Normal and Diabetic Subject*

Muscles	1. Normal: Age 42; Height 170 Cm. (5 Ft. 7 In.); Weight 48 Kg. (106 Lbs.); Strength in Kg.	2. Diabetic: Age 40; Height 177 Cm. (5 Ft. 10 In.); Weight 50 Kg. (110 Lbs.); Strength in Kg.
Pectoral.....Left.....	26	19
Right.....	27	23
Wrist flexor.....Left.....	16	16
Right.....	16	16
Forearm flexor..Left.....	23	20
Right.....	26	23
Thigh abductor..Left.....	12	15
Right.....	14	16
Thigh adductor..Left.....	11	16
Right.....	11	16
Total strength.....	1,030	1,020
Strength-weight ratio.....	21.6	20.4

examination and both had normal urines. As one saw the two men, the striking difference between them was in their mental attitude. The normal man was eager, quick in his motions and working mentally at top speed. The diabetic man, in contrast, was not eager, was slow in all his motions and was working mentally at a slow speed. The basal metabolic rate of the normal man was known to be normal; Joslin informs us that the metabolic rate of the diabetic patient was minus 18 at about the time the strength test was made. Therefore, the chief objective difference between the two men lay in the difference of their basal metabolism. One cannot but wonder from such a comparison how much the factor of suboxidation has to do with producing the clinical picture of chronic diabetes where a low metabolism is found so frequently.

On the whole, these preliminary observations on the strength of diabetic patients brought out the following points: the majority of the men and women of the series tended to be considerably weaker than normal persons but without any specific weakness of any of the muscle

groups studied. The diabetic men were not only weak because they tended to be underweight, but were weaker than normal in proportion to their diminished weights. The women, on the other hand, appeared to be weak solely because they were undernourished and tended to be normally effective in proportion to their body weights. A comparison between a normal thin man and a chronic well treated diabetic patient of approximately equal size and age showed that the two subjects had the same amount of strength; the normal subject, with normal basal metabolic rate, was much more alert and keen than the diabetic subject who with a metabolic rate, was sluggish mentally and physically. This observation suggested that other factors than chronic inanition may play a part in producing the clinical picture of long-standing diabetes.

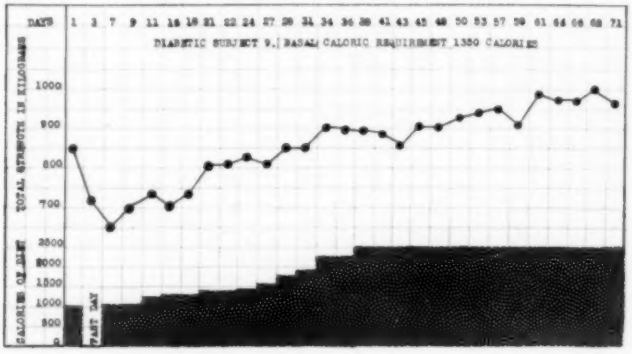

Chart 3.—The relation between the calories of the diet and strength in a diabetic patient.

We [11] have already shown by illustrative strength curves that certain patients with severe diabetes may gain a great deal of measurable strength during treatment. It is of interest to analyze how strength is gained. The most important single factor which gives a diabetic patient strength appears to be the total calories of the glycosuria free diet utilized. This point is illustrated by Chart 3.

The patient was a man, aged 38, with diabetes of about nine months' duration. When he entered the hospital he had lost about 50 pounds (22 kg.) in weight and was very weak.

During the interval in which he received less calories than his basal requirement, he failed to gain strength and even lost slightly. It was not until he was given calories well above his basal requirements that he gained perceptibly, and it appeared to take several days for him to

11. Fitz, Reginald, and Murphy, W. P.: Insulin as an Investment for the Patient with Diabetes Mellitus, J. A. M. A. **82**:435-438 (Feb. 9) 1924.

recover the strength which was lost during the period of greatest undernutrition. We have made confirmatory observations on the weakening effect of undernutrition in several other cases; on this account we now desugarize the patients with severe diabetes with insulin as soon as they come into the hospital, and no longer use very low calory diets for more than a day or two, as the strength lost by such treatment seems out of proportion to the tolerance gained.

Unfortunately we have not succeeded in making any critical observations on the strength yielding properties of diets variously balanced in respect to their carbohydrate, protein and fat fractions. Such evidence as we have, however, suggests that weak diabetic patients will gain strength satisfactorily when given diets containing about 1 gm. of

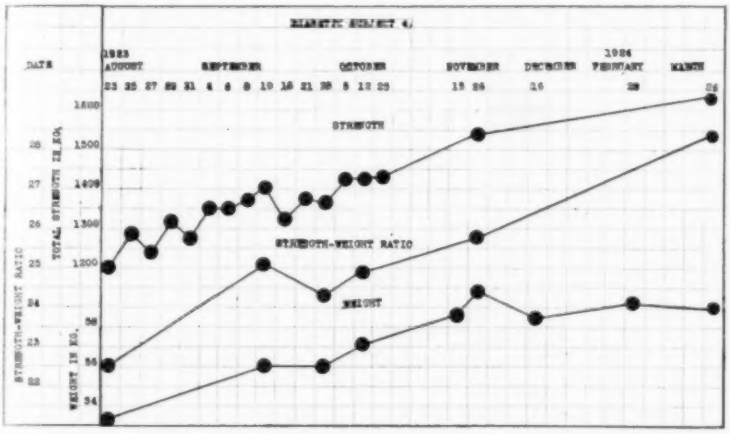

Chart 4.—The relation between strength and weight in a well treated diabetic patient.

protein and about 45 calories per kilogram of body weight. It seems to make but little difference in what form the calories are given so long as the fat proportion is not enough in excess to cause acidosis, and so long as the urine remains sugar-free.

From the point of view of strength, it appears that the best treatment for a diabetic patient should combine an adequate diet with adequate physical exercise, so that as the patient gains weight he gains a more than proportional amount of strength and thus has an increasing strength-weight ratio. One of the temptations offered by insulin is the possibility of fattening diabetic patients rapidly. We have three patients who became fat under insulin treatment, gaining weight more rapidly than they gained strength, and these patients do not seem as well or as physically efficient now as those that have gained strength

more rapidly than they have gained weight. On this account we do not believe in using very high calory diets and large amounts of insulin, in order to obtain an immediately striking therapeutic result, but prefer to have our patients take less to eat, use smaller amounts of insulin and to gain weight and strength slowly. The strength curve of a patient under observation for seven months and treated conservatively in this fashion is recorded in Chart 4.

The patient was a man, aged 20, 178 cm. (5 feet 10½ inches) tall, weighing 53.4 kg. (117 pounds) in August, when we first saw him. His basal caloric requirements at that time were 1,600 calories, and at the beginning of treatment the patient was about 40 pounds (18 kg.) under standard weight. Fortunately his strength had not been much depleted during the eight months he had diabetes, so that his physical condition was fairly good. Since he came to the Brigham Hospital he has taken each day a diet containing about 2,500 calories and 60 gm. of protein. On this diet he has gradually gained 6 kg. (13 pounds) in weight. With this gain in weight, which still leaves him more than twenty-five pounds under standard weight, he has increased his strength markedly and now has a very high strength-weight ratio. It so happens that he is an insurance broker forced to do considerable walking each day in his business, and thus he has been compelled by economic reasons to take an adequate amount of exercise. He has gained but little weight during the last three months, although his strength and strength-weight ratios have increased steadily. When we last saw him he felt in perfect health, was able to work as hard as he chose without undue fatigue and he was stronger than our average normal man. We have advised this patient to keep his weight at about its present level and have warned him against gaining more than a few extra pounds.

SUMMARY

On the whole, from these studies on the muscular efficiency of patients with diabetes we have obtained evidence confirming the observations of Williams and of Miles and Root. The strength of most diabetic patients is appreciably less than normal, but can be made to approach normal by proper diet and physical therapy. The total calories of the diet rather than the fractions of carbohydrate, protein or fat, seem of greatest importance in adding strength.

Since there is no selective weakness of any particular muscle group which characterizes diabetes, any general form of exercise which will bring all the muscles into play is indicated from the point of view of physical therapy.

Undernutrition for any length of time is weakening and should not be recommended for more than a day or two as the strength lost

by such treatment is out of proportion to the tolerance gained. The best treatment for a diabetic patient should combine diet and physical exercise, so that as the patient gains weight he gains a more than proportional amount of strength and an increasing strength-weight ratio. Diabetic patients should not be fattened rapidly with insulin and high calory diets. Such patients do not become as physically efficient as patients who gain weight more gradually on a lower diet and less insulin, and who remain thin but relatively strong with high strength-weight ratios.

Book Review

GENERAL AND EXPERIMENTAL PATHOLOGY. By HERMANN PFEIFFER, Professor at the University of Graz. Pp. 594, 50 illustrations, 8 color plates. Berlin and Vienna, Urban and Schwarzenberg, 1924.

An ever widening foundation of biochemistry, biophysics and physiology form the basis of our understanding of pathologic processes and clinical manifestations of disease. To present an even superficial view of this vast fabric of interrelated basic phenomena in a single volume seems an almost hopeless task, the more so when it is to be made useful for students of medicine rather than the more mature. Krehl succeeded in a singularly striking fashion, due, no doubt, to his marvelous grasp of the material. We now possess three additional efforts in the same direction, those of Herring, of Ludke and Schlayer, and of Pfeiffer, here reviewed. In its subject matter Professor Pfeiffer's work is also a pathologic physiology.

There can be no doubt as to the importance of the subject or of the value of the systematic and orderly treatment of the material for the student. Teachers of medicine realize only too well that much of the most valuable and important "borderline" knowledge that the student should possess is never presented to him in any organized series of lectures, certainly never from the medical point of view. This whole group of German texts seems of particular value in bridging this gap; it is unfortunate that they may seem so formidable that the medical student would hardly find the time to use them.

Pfeiffer's book covers the extrinsic causes of disease, inflammation and fever, immunity, the blood diseases and circulation, respiratory alterations, metabolism, the glands of internal secretion and experimental tumors. The general character of the work is exemplified in a chapter of 110 pages on internal secretion, in which a most objective summary is presented; the chapter on "Inflammation" and on "Fever" are particularly readable.

The investigator will perhaps miss references, purposely omitted to permit condensation, but will be rewarded by an excellent review of the best work in the fields covered. It is to be regretted that we have no English counterpart of this and the similar books; they would be of great value to the serious medical student in his transition from the laboratory to the clinic, a transition which in the majority of our medical schools is harmful because of its abruptness.

To the fact that the text has been written by a single person must be credited the absence of reduplication and redundancy in the book, and the fact that the proper proportion has been maintained in the various sections.